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*SYNTHETIC STUDIES IN*  
*TECOMA STANS ALKALOIDS AND RELATED COMPOUNDS*

*by*

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*A thesis submitted to the  
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## ABSTRACT

The chemistry of *Tecoma stans* and cyclopentanoid monoterpene alkaloids is reviewed. A brief review of the chemistry of the related compounds and of 9-azasteroids is also included.

Several methods for the construction of a perhydropyridane system have been investigated.

A synthesis of 2:4-dimethyl-1:2:3:4:5:7-hexahydro-6H-2-pyridin-2-one is given, together with the syntheses of 1:5-dimethyl-3-carboethoxy-4-piperidone and N-phenyl-3-carbomethoxy-4-piperidone.

Alkylation of the basic keto-esters (e.g. 1:5-dimethyl-3-carboethoxy-4-piperidone) has been achieved in higher yields than reported in the literature.

A synthesis of 1:5-dimethyl-3-cyanomethyl-4-piperidone and its conversion to 1:5-dimethyl-3-cyanomethyl-4-chloropiperidine is described together with a synthesis of the ethylene ketal of N-methyl-3-carboethoxymethyl-4-piperidone.

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I N T R O D U C T I O N

## NOMENCLATURE

Wherever possible, compounds are named according to "Handbook for Chemical Authors", 1961, or "Chemical Abstracts". Arabic numerals will be used for the sake of simplicity.



*The chemistry of Tecoma stans and cyclopentanoid  
monoterpene alkaloids.*

The presence of alkaloids in *TECOMA STANS JUSS* was first noted by Boersma<sup>1</sup> in 1899.

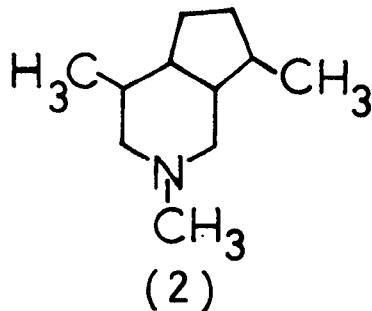
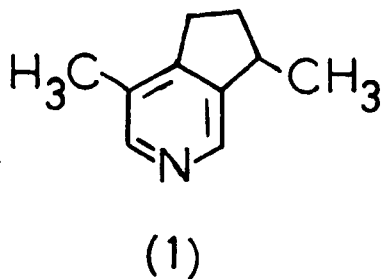
In 1959, Hamouda and Motawi<sup>2</sup> reported the presence of a liquid alkaloid ----- *TECOMINE*, in the same plant. This base,  $[\alpha]_D^{23} -20$ , exhibited a carbonyl group in the IR spectrum, formed a picrate, m.p.  $154^\circ$ ; a methiodide, m.p.  $265^\circ$  suggesting  $C_{11}H_{17}ON$  as the empirical formula of the free base; and a 2:4-dinitrophenyl-hydrazone, m.p.  $260^\circ$ .

In 1962, Jones et al,<sup>3</sup> while working on the same plant, found an alkaloid having the same empirical formula as tecomine but possessing quite different physical properties, and hence named it *TECOMANINE*. This base is colourless unstable liquid, b.p.  $125^\circ/0.1$  mm,  $[\alpha]_D^{24} -175^\circ$  (c 1.17,  $CHCl_3$ )  $\lambda_{max}^{EtOH}$  226 m $\mu$  (log  $\epsilon$  4.10),  $\lambda_{max}^{EtOH \text{ acid}}$  223 m $\mu$  (log  $\epsilon$  4.13);  $\nu_{max}^{CHCl_3}$  1700, 1620  $cm^{-1}$  ----- characteristic of  $\alpha:\beta$ -unsaturated cyclopentenone. It forms a picrate,  $C_{17}H_{20}O_8N_4$ , m.p.  $179.5 - 180.5^\circ$ ; and a methiodide,  $C_{12}H_{20}ONI$ , m.p.  $240 - 2^\circ$  (dec.).

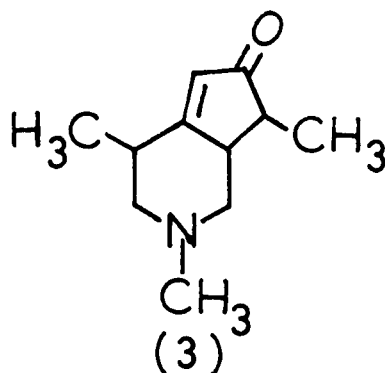
The NMR spectrum ( $CDCl_3$ ) of the compound revealed the presence of an olefinic proton at  $\delta = 5.95$ , an N-methyl group at  $\delta = 2.75$  and two C-methyl groups as doublets centred at  $\delta = 1.12$  and  $\delta = 1.07$ .

Reduction of tecomanine with  $PtO_2$ /acetic acid, yielded a mixture of saturated ketones. Huang-Minlon reduction of the mixture gave three bases, which on dehydrogenation over Pd-C afforded dl-actinidine (1). Reduction with Pd-C/ethanol gave dihydro tecomanine, this when subjected to Huang-Minlon reduction afforded one of the

possible isomers of skytanthine (2).

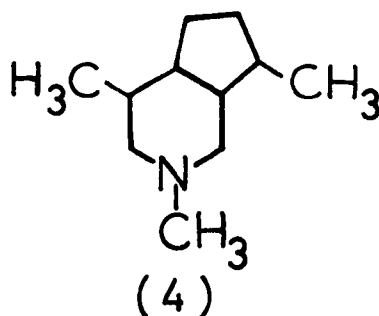


All these reactions and many others led to the suggestion of the structure (3) for TECOMANINE.

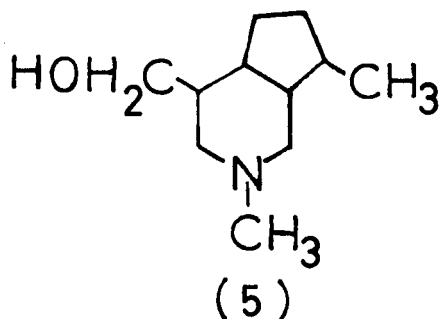


In 1963, another alkaloid TECOSTANINE was isolated from the same plant by Hammouda et al.<sup>4,5</sup>

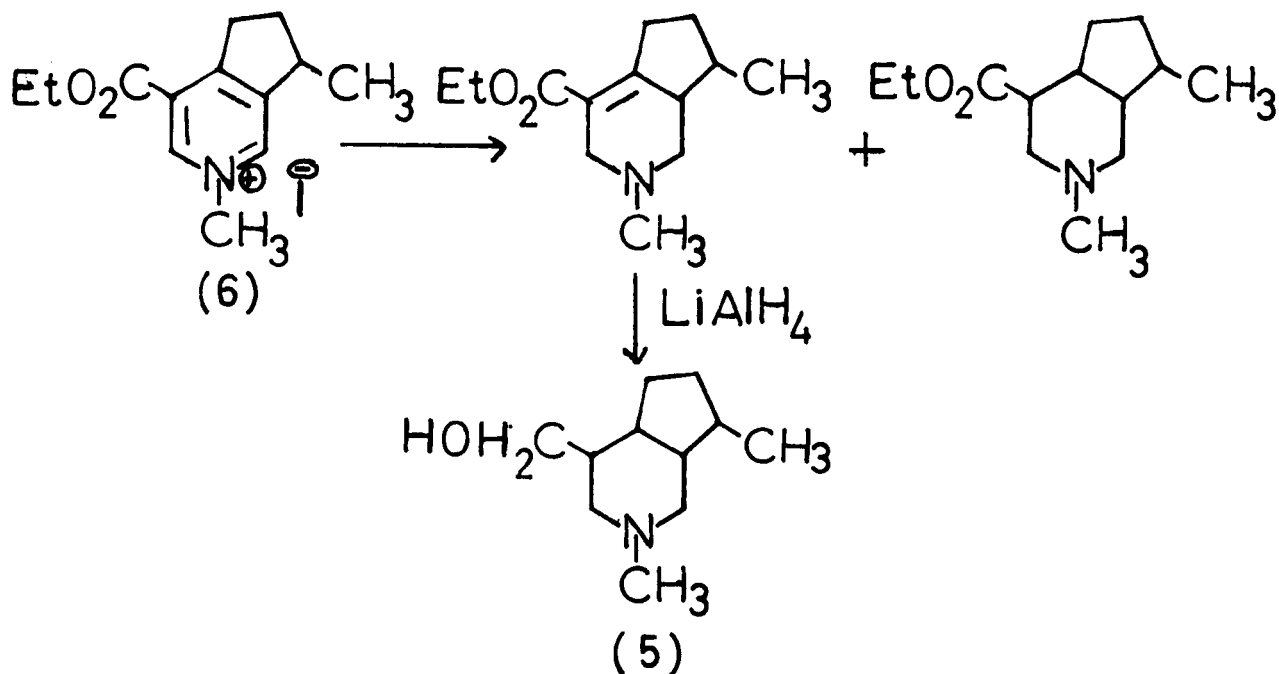
This is a solid m.p.  $85^{\circ}$ ,  $[\alpha]_D^{20}$  0, forms a liquid O-acetyl derivative,  $C_{13}H_{23}O_2N$ ; and also a colourless viscous tosylate that gave deoxytecstanine,  $C_{11}H_{21}N$  (4) with  $LiAlH_4$ /ether and this (4) on dehydrogenation over Pd-C gave actinidine (1). Thus



deoxytecstanine (4) was thought to be a stereoisomer of skytanthine, but found to be neither identical with any of the known stereoisomers of skytanthine<sup>15</sup> nor with the deoxyhydrogenated derivative prepared by Jones et al.<sup>3</sup> However TECOSTANINE was given the 11-hydroxy skytanthine structure (5).



This was supported by UV, IR, NMR and MASS spectra. Tecostanine has recently been synthesised<sup>6</sup> starting from the synthetic N-methiodide of pyridine ester (6). The methiodide was reduced with Sn-HCl/ethanol,

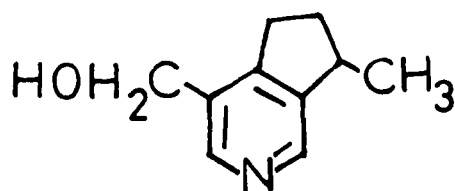


yielding a mixture of stereoisomeric N-methyl piperidine esters together with a tetrahydropyridine ester. Reduction of the unhydrogenated ester mixture with  $\text{LiAlH}_4$  yielded the N-methyl piperidine alcohols of tecostanine (5) type. Gas chromatography indicated four components, one of the minor peaks c. 5% of the mixture had a retention time comparable with that of an authentic specimen of tecostanine (5); however, the major components of the synthetic mixture were diastereoisomers of the natural product.

Chromatography of an extract from the leaves of *Tecoma stans* or working up the mother liquors from the crystallisation of tecostanine (5) furnished TECOSTIDINE.<sup>7</sup>

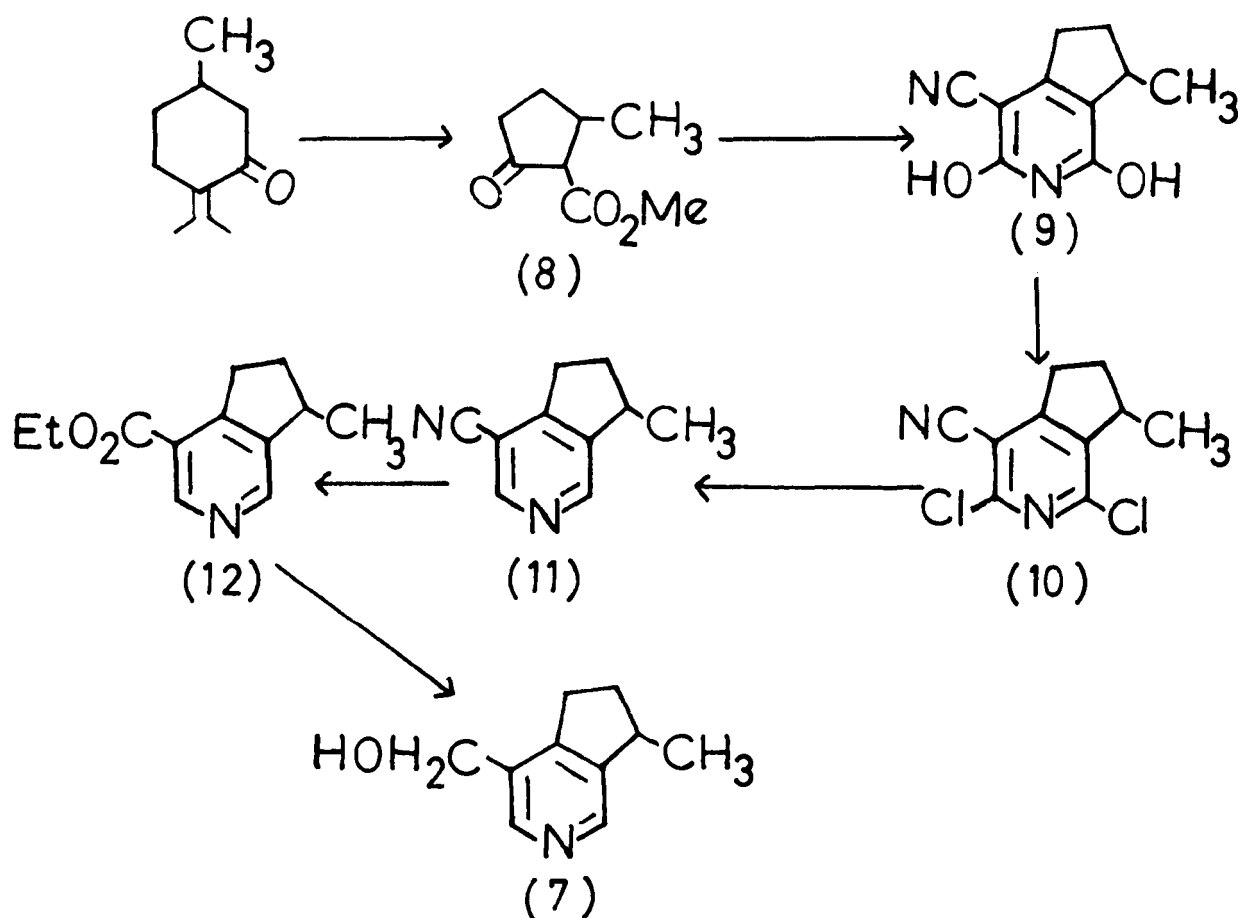
This is a viscous liquid, darkens in light  $[\alpha]_D^{22} -4^\circ$  (C 1.221,  $\text{CHCl}_3$ ). It forms a picrate m.p.  $152-3^\circ$  and an O-acetyl derivative but does not form a tosylate and cannot be hydrogenated catalytically at atmospheric pressure in ethanol.

The NMR, IR, UV and MASS spectra of the natural and deuterated compound were compared. These data and many others pointed to the 11-hydroxy-actinidine structure (7) for tecostidine.



(7)

This structure (7) has been confirmed by synthesis.<sup>6</sup> The starting material ——— 2-methoxy-carbonyl-3-methyl-cyclopentanone (8) was derived from D(+)-pulegone via methyl pulegenate. Condensation of (8) with cyano-acetamide in the presence of pyridine or KOH yielded the

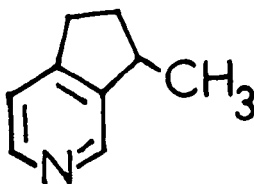


dihydroxy pyridine derivative (9), and this with  $\text{POCl}_3$  gave the dichloro-compound (10) which on hydrogenolysis in the presence of Ir-catalyst was converted into the cyanopyridine (11). Hydrolysis of the latter with a basic Amberlite resin afforded the amide which was transformed into the ethyl ester (12) by the action of ethanol/HCl. Reduction of this ester (12) with  $\text{LiAlH}_4$  gave D(+)-11-hydroxy actinidine (7).

On gas chromatography this synthetic compound (7) had the same retention time as an authentic specimen of (-)-tecostidine and the NMR spectrum was identical with that reported for the natural product.

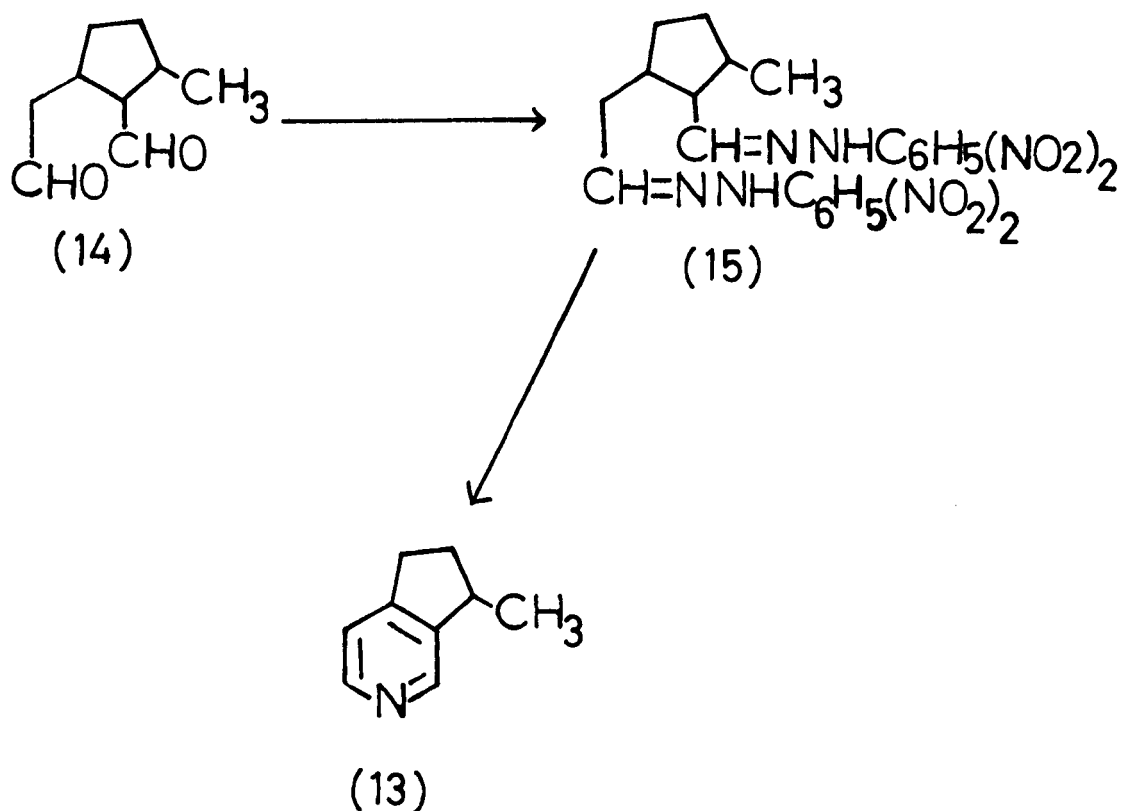
This synthesis of D(+)-11-hydroxyactinidine confirms that the naturally occurring enantiomer, (-)-tecostidine has the same absolute configuration as L-(-)-actinidine.

Another alkaloid, NOR-ACTINIDINE,<sup>8</sup> of *Tecoma stans* Juss was shown to be a pyridine derivative  $[\alpha]_D^{24} = +3^\circ$  (2.34 C in  $\text{CHCl}_3$ ). It formed a picrate, m.p. 116-7°, indicating an empirical formula,  $\text{C}_9\text{H}_{11}\text{N}$  for the free base. The free base regenerated from the picrate by the action of  $\text{LiOH}$ , showed  $\lambda_{\text{max}}^{\text{EtOH}}$  259.5 mμ and 267 mμ ( $\log_{10} \epsilon$  3.05). The IR spectrum in the region  $900 \text{ cm.}^{-1}$  to  $650 \text{ cm.}^{-1}$  was similar to that of 3:4-lutidine. The NMR spectrum of the picrate showed the presence of two α-pyridine protons; a singlet at 8.75 p.p.m., overlying one-half of a doublet centred at 8.8 p.p.m. ( $J = 6 \text{ c.p.s.}$ ). A β-pyridine proton was detected at 8.0 p.p.m. ( $J = 6 \text{ c.p.s.}$ ) and a three proton doublet at 1.55 p.p.m. ( $J = 6 \text{ c.p.s.}$ ). Thus the alkaloid was thought to have the structure (13).



(13)

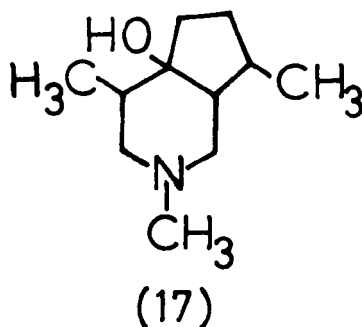
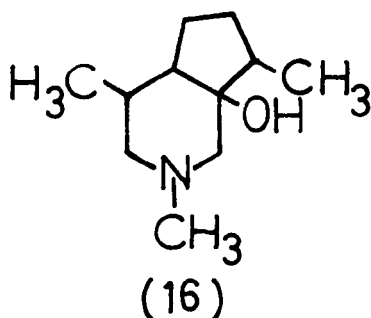
This structure (13) has been synthesised.<sup>9</sup> Cis,cis-2-formyl-3-methyl-cyclohexyl acetaldehyde (14) obtained as a degradation product from



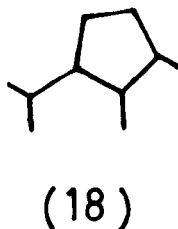
asperuloside was converted into its bis-2:4-dinitrophenylhydrazone (15). This (15) on treatment with conc. HCl/acetic acid (gl.) gave nor-actinidine (13). The picrate of the synthetic nor-actinidine (13) had m.p. 115.5-6° and did not depress the melting point of the picrate of the natural alkaloid. The IR spectra of the two picrates were identical. No figures were mentioned for the optical rotation of the synthetic compound (13) and thus the configuration of the alkaloid from *Tecoma stans* is not known.



Dickinson<sup>10</sup> reported the presence of another alkaloid in *Tecoma stans* Juss. It formed a picrate, m.p. 170-170.5°, indicating  $C_{11}H_{21}ON$  as the empirical formula of the free base. Regenerated from the picrate, the base sublimed at 110°/0.25 mm to give a solid, m.p. 91-2°. The NMR spectrum of this compound showed two C-methyl doublets at 0.9 p.p.m. The compound was transparent in the UV above 220 mμ and the IR spectrum showed a band at 3609  $cm^{-1}$ , indicating the presence of a tertiary alcohol. The compound was thought to be a **HYDROXYSKYTANTHINE** having the structure (16) or (17), on the basis of the above data and many other reactions.



All the compounds from *Tecoma stans* mentioned so far, though differ in structure but are identical, at least, in one respect — the presence of a cyclopentanoid monoterpene skeleton (18) except for nor-actinidine (13) in which the C-methyl group on the side-chain

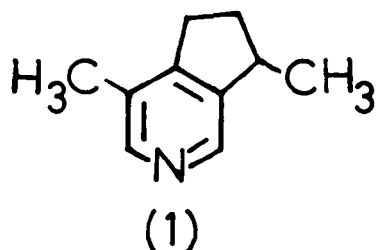


has been eliminated somehow and in tecomanine (3) in which the keto group seems to have been derived from the methyl instead of the carbonyl carbon of acetic acid.<sup>3</sup>

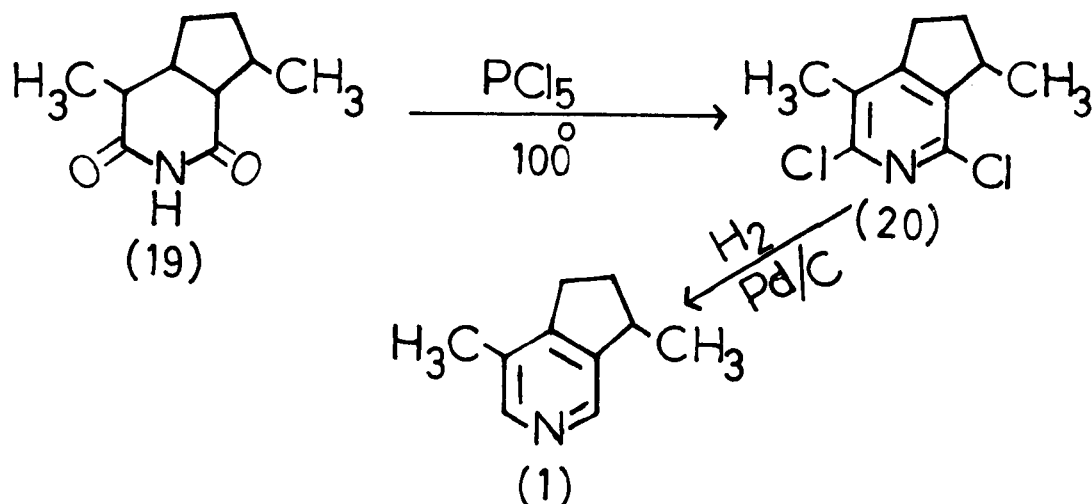
The compounds which contain the carbon skeleton (18), are known as the cyclopentanoid monoterpenes<sup>11</sup> \_\_\_\_\_ and hence these alkaloids, in general, are referred to as the CYCLOPENTANOID MONOTERPENE ALKALOIDS.

These Tecoma stans alkaloids (3, 5, 7, 13, and 16 or 17) are not the only cyclopentanoid alkaloids known \_\_\_\_\_ the first of this series being ACTINIDINE isolated together with MATATABILACTONE in 1959 by Sakan et al.<sup>12a</sup> from a Japanese plant, *Actinidia polygama* (Miq.) \_\_\_\_\_ a plant especially liked by the Felidae animals.

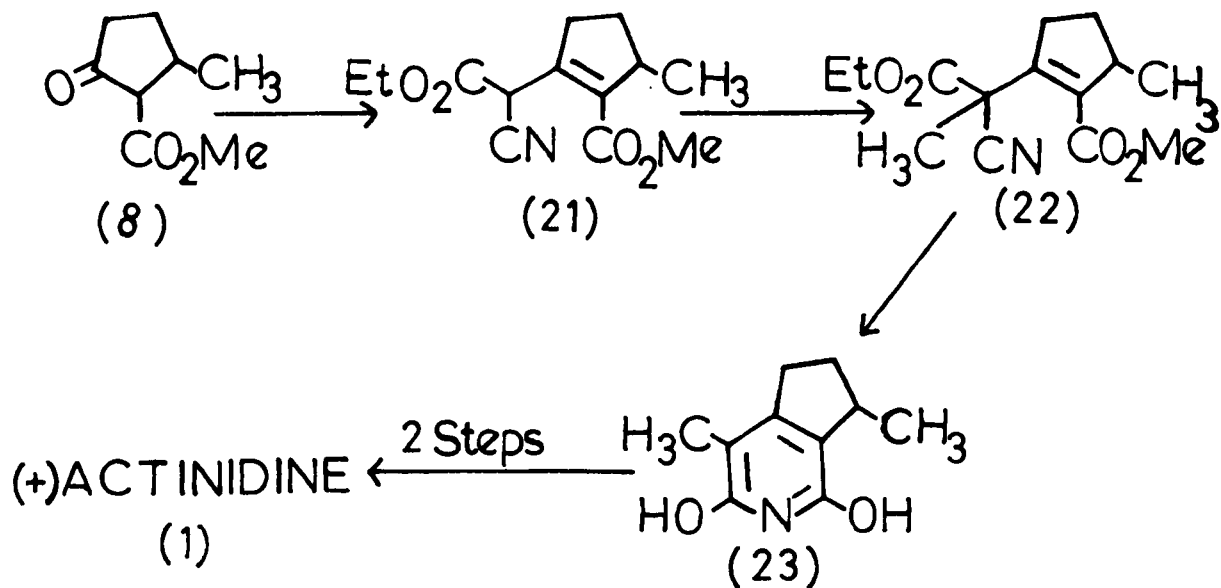
Actinidine,  $C_{10}H_{13}N$ , b.p.  $100-3^{\circ}/9$  mm.,  $[\alpha]_D^{11} -7.2$  (C 17.54  $CHCl_3$ ) forms a picrate, m.p.  $143^{\circ}$ . Actinidine was assumed to be a pyridine base from its colour reactions (violet to 2:4-dinitrochlorobenzene and alkali) and UV,  $\lambda_{max}^{EtOH}$  262 m $\mu$  ( $\epsilon = 2,400$ ) and IR spectra,  $\nu_{C=N}$  6.30  $\mu$  (liquid). These properties together with many others indicated the structure (1).



Actinidine (1) has been synthesised from nepetalinic acid imide (19).<sup>12a</sup>



Another synthesis of actinidine (1) has been reported<sup>12b</sup> starting from (+)-pulegone through methyl puleginate which was converted to 2-methoxycarbonyl-3-methyl cyclopentanone (8). The condensation product (21) was

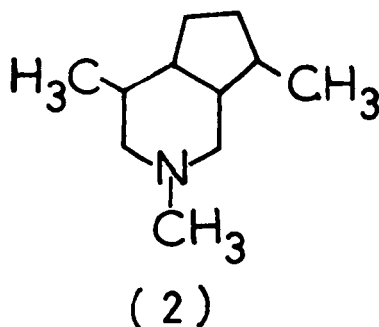


treated, in presence of NaOEt/ethanol, with methyl iodide and the methylated diester (22) was hydrolysed with acid or alkali to the dihydroxypyridine derivative (23), the chlorination of which and the successive catalytic hydrogenation of the dichloro compound furnished actinidine (1). The purified base (through picrate) b.p. 88-90°/5 mm. gave a value of  $[\alpha]_D^{15} +16.1^{\circ}$  (C 5.52 CHCl<sub>3</sub>) and the identical IR

spectrum with the natural alkaloid. Although the absolute values of optical rotation of the two actinidines were not equal, the synthesised one was likely to be in a more pure state.

The second cyclopentanoid monoterpene alkaloid \_\_\_\_\_ SKYTANTHINE, was obtained from *Skytanthus acutus* Meyen, a Chilean member of Apocynaceae. The chemistry of this alkaloid was studied by Djerassi et al.<sup>13</sup> in America and Cassinovi et al.<sup>14</sup> in Italy.

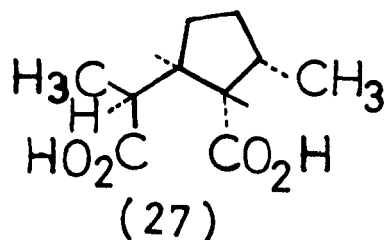
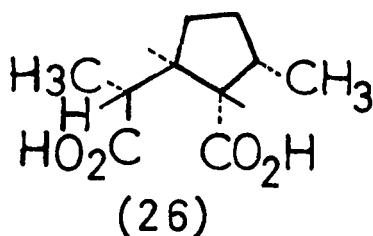
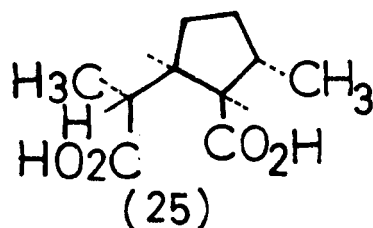
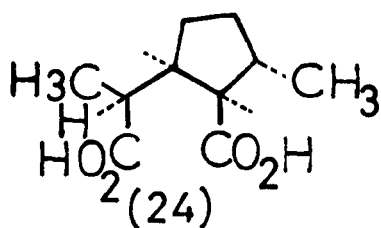
Skytanthine is an optically active liquid,  $[\alpha]_D^{+42^\circ}$ , b.p.  $54^\circ/1.5$  mm. of the empirical formula  $C_{11}H_{21}N$ , having two C-methyl and one N-methyl groups. The IR spectrum was of a simple nature with no characteristic absorption for any functional group and there was no absorption in the UV region and the structure was deduced to be (2) as a result of NMR studies and Hofmann degradation.



Skytanthine (2) on dehydrogenation over Pd-black, furnished an optically inactive pyridine derivative which was shown to be identical with racemic actinidine (1) through a comparison of the melting points and the IR spectra of the respective picrates.

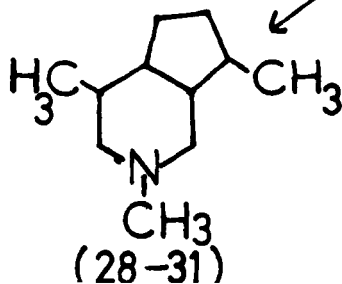
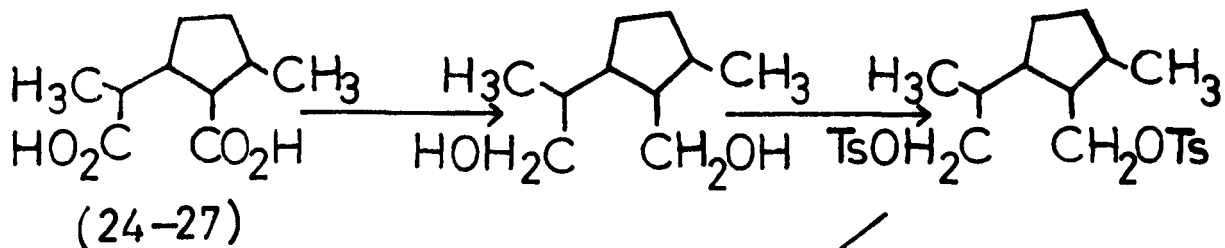
The natural skytanthine (2) isolated above was shown to be a mixture of three diastereoisomers \_\_\_\_\_  $\alpha$ -,  $\beta$ -, and  $\delta$ -skytanthines.

These diastereoisomers have been synthesised<sup>15</sup> by stereospecific conversion of  $\alpha$ -,  $\beta$ -,  $\gamma$ - and  $\delta$ -nepetalinic acids<sup>16</sup> of firmly established absolute configuration (24 - 27).

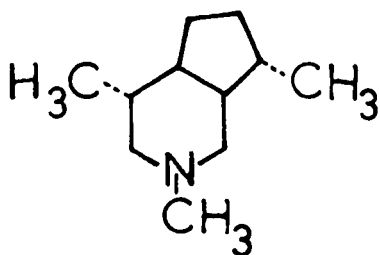


These acids have been extensively used as reference compounds in the correlation of the structure and stereochemistry of the cyclopentanoid monoterpene alkaloids and related compounds.

For the syntheses of skytanthines, nepetalinic acids (24 - 27) were reduced to diols with  $\text{LiAlH}_4$  and then converted to bis-tosylates which were purified through silica gel chromatography. Cyclisation to the

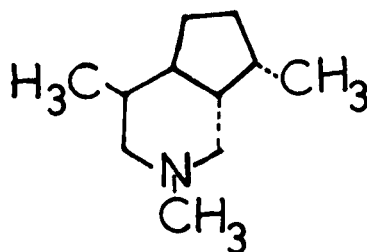


corresponding alkaloids was accomplished by heating the bistosylates at  $100^{\circ}$  for 18 hrs. in a sealed vessel containing an excess of methylamine.



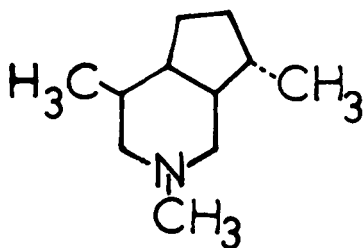
$\alpha$ -SKYTANTHINE

Picrate, m.p.  $120^{\circ}$   
(28)



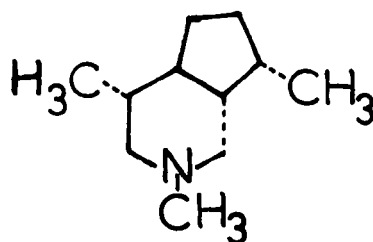
$\beta$ -SKYTANTHINE

Picrate, m.p.  $135^{\circ}$   
(29)



$\delta$ -SKYTANTHINE

Picrate, m.p.  $139^{\circ}$   
(31)



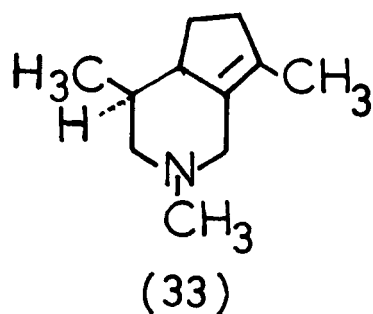
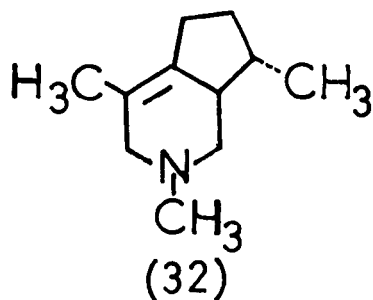
$\gamma$ -SKYTANTHINE

Picrate m.p.  $162^{\circ}$   
(30)

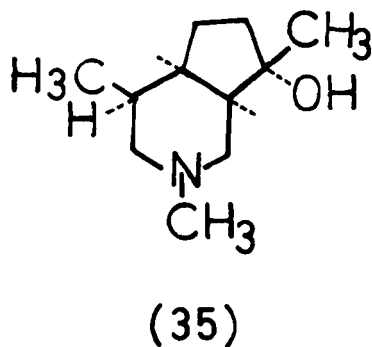
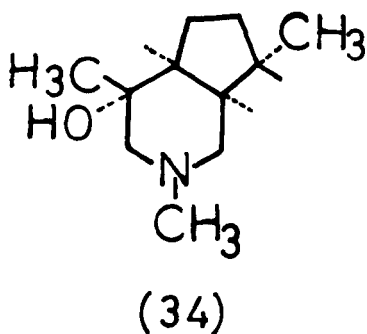
The remainder of the volatile alkaloid material consisted of two compounds. Only one of those formed a picrate,<sup>17</sup> m.p.  $127^{\circ}$ . The free base was shown to be unsaturated. From a study of its NMR spectrum and by VPC comparison of its reduction product with the known skytanthines<sup>15</sup> (28 - 31), it was thought to have been derived from

$\delta$ -skytanthine (31) and thus was formulated as (32) or (33)

DEHYDROSKYTANTHINE.

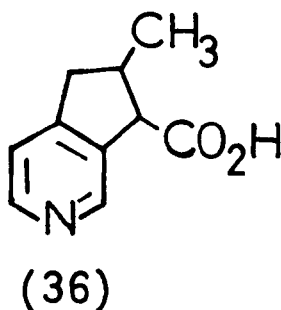


The non-volatile fraction from the leaves of *Skytanthus acutus* Meyen yielded a crystalline alkaloid,<sup>18</sup> m.p. 93°. This compound was shown to be an alcohol. On dehydration with  $\text{SOCl}_2$ , it gave an unsaturated base identical with the dehydroskytanthine (32) or (33). Recently, this compound was reinvestigated<sup>19</sup> and, in fact, found to be a mixture of two isomeric HYDROXYSKYTANTHINES (34) and (35).

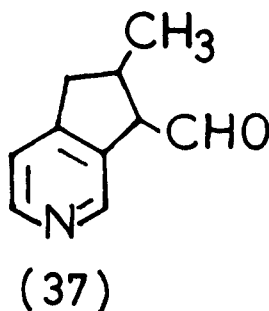


Hydroxyskytanthine (34) has m.p.  $94-5^{\circ}$ ,  $[\alpha]_D +38.5$  (cyclohexane),  $+35.8$  (methanol) and hydroxyskytanthine (35) which was obtained in very small yield (0.001%), has m.p.  $119-120^{\circ}$ ,  $[\alpha]_D -38.5$  (methanol). The two structures, (34) and (35), are based on a detailed comparative study of NMR and MASS spectra of the two compounds.

Two alkaloids ——— PLANTAGONINE and INDICAIN were isolated from the plant *Pedicularis olgae*.<sup>20</sup> Plantagonine had a UV maximum characteristic of alkaloids of the pyridine group at 270 m $\mu$  ( $\log \epsilon$  3.12) and a C-methyl doublet at  $\delta = 1.15$  in NMR spectrum. A study of the MASS spectra of the compound and many other reactions indicated the structure (36) for plantagonine.



Indicain which fragmented in the same way as plantagonine in the MASS spectral analysis and on oxidation yielded plantagonine (36) was obviously the corresponding cyclic amine aldehyde (37).





From the dried roots of *Valeriana officinalis*, a crystalline quaternary base, <sup>21</sup> m.p. 201 - 3°,  $[\alpha]_D^{22} +50.5$  (methanol), was isolated as the chloride,  $C_{18}H_{22}ONCl$ .

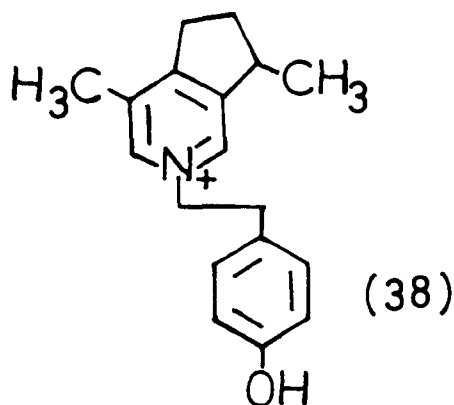
This quaternary base exhibited  $\nu_{\max} 3400 - 2900 \text{ cm.}^{-1}$ , indicating strong hydrogen bonding; 1635 and 1615  $\text{cm.}^{-1}$ , possibly aromatic; and at 1585, 1515 and 1485  $\text{cm.}^{-1}$ . The strong absorption at 837  $\text{cm.}^{-1}$  was thought to be due to a 1:4-disubstitution pattern in the aromatic ring.

UV absorption maxima in acid and neutral solution were found to be at  $\lambda_{\max} = 222 \text{ m}\mu$  ( $\epsilon = 12000$ ) and  $\lambda_{\max} = 267 \text{ m}\mu$  ( $\epsilon = 5500$ ); and in alkaline solution at  $\lambda_{\max} = 242 \text{ m}\mu$  ( $\epsilon = 16000$ ) and  $\lambda_{\max} = 292 \text{ m}\mu$  ( $\epsilon = 3000$ ). The shift indicated the presence of a phenolic group which was supported by acetylation that gave a product with an IR absorption at 1760  $\text{cm.}^{-1}$  within the region of phenolic esters.

The NMR spectrum in  $(CD_3)_2SO$  solution indicated a total of 22 protons; two pyridine protons at  $\delta = 8.90$  and 8.83 p.p.m., the two pairs of benzenoid protons at  $\delta = 7.04$  and 6.73 p.p.m., one methylene triplet (attached to ammonium and split by another methylene) at  $\delta = 4.73$  p.p.m., one aromatic C-methyl singlet (attached probably to pyridine ring) at  $\delta = 2.34$  p.p.m., and one aliphatic C-methyl doublet at  $\delta = 1.23$  p.p.m., and the rest of the aliphatic protons formed a broad band at  $\delta = 3.5 - 1.5$  p.p.m.

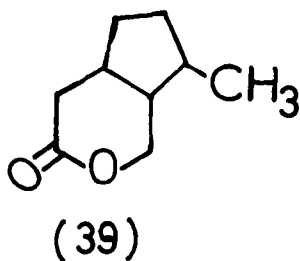
The MASS spectrum showed no molecular ion peak because the compound was a salt. The highest peaks located at  $m/e$  337 and 336; and other strong peaks at 268, 267, 147, 132, 121, 120, 107, 91 and 77.

These data and many other reactions led to the suggestion of the

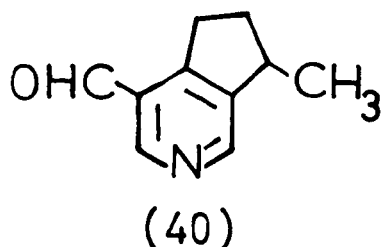


structure (38) for the compound.

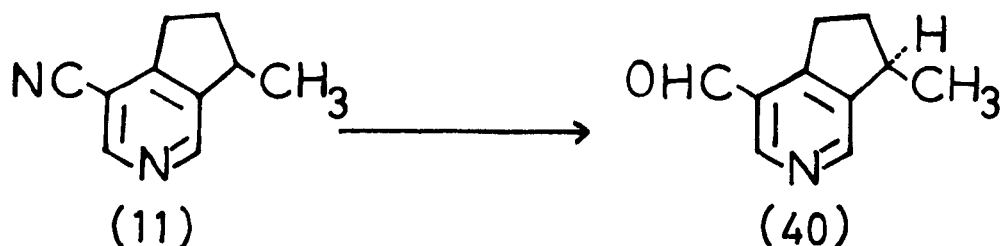
Recently BOSCHNIAKINE — another cyclopentanoid monoterpene alkaloid has been isolated<sup>22</sup> along with boschnialactone (39), from *Boschniakia rossica* Hult belonging to the family Orobanchaceae and also liked by Felidae animals.



Boschniakine occurs as a fragrant liquid, b.p. 80 - 90°/3 mm,  $[\alpha]_D^{20} +21.02^\circ$  and has got the empirical formula,  $C_{10}H_{11}ON$ . It forms a picrate, m.p. 126.5 - 128° and a semicarbazone, m.p. 227 - 8°(dec.). The base obtained by Huang-Minlon reduction and its picrate were identical with actinidine and its picrate in IR spectra. Since the UV and IR absorption maxima -  $\lambda_{max}$  239, 268 and 282 m $\mu$ ,  $\nu_{max}$  3050, 2725, 1700 and 1580  $cm^{-1}$  suggest the presence of an aldehyde group conjugated with a pyridine ring, the structure (40) was assigned to boschniakine.



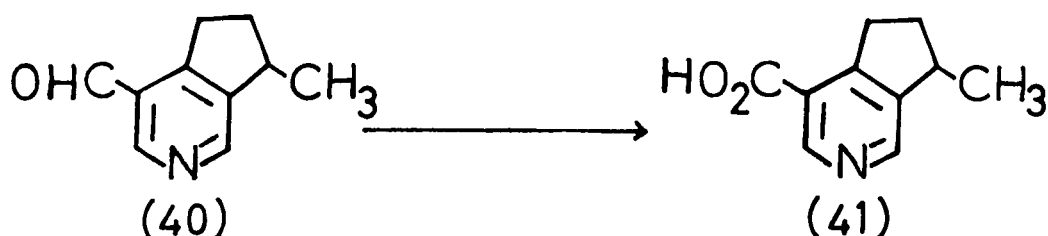
This structure (40) has been confirmed by synthesis.<sup>22</sup> Starting with 2-methoxy carbonyl-3-methyl cyclopentanone (8) derived from D(+)-pulegone via methyl puleginate, the cyanopyridine derivative (11) was obtained via the dihydroxy pyridine derivative (9). The cyano-pyridine derivative (11) was reduced with a large excess of stannous chloride/HCl and the resulting aldimine-stannic chloride complex was submitted to



steam distillation whereby hydrolysis was effected together with the isolation of the product ——— boschniakine (40),  $[\alpha]_D^{20} +28.4^\circ$ . The UV and IR spectra and the specific rotation of this substance (40) were identical with those of the natural product.

Boschniakinic acid,  $C_{10}H_{11}O_2N$ , m.p.  $215 - 20^\circ$  (dec.) was obtained from the high boiling fraction by the distillation of boschniakine. Its IR spectrum exhibited absorption bands at 2450, 1950, 1700, 1602 and  $1575\text{ cm}^{-1}$  which were consistent with a pyridine carboxylic acid structure.

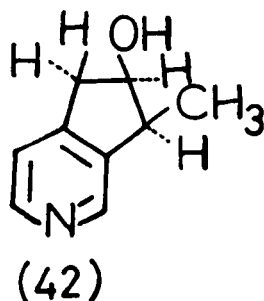
This acid seemed to be an auto-oxidation product of boschniakine (40) and its structure (41) was confirmed by the oxidation of boschniakine (40)



with silver oxide.

More recently some studies have been made on *Rauwolfia verticillata* (Lour) Bail.<sup>23</sup> of Hong Kong, belonging to the family Apocynaceae, and as a result, a new cyclohexanoid monoterpene alkaloid ——— RW47, has been isolated.

The alkaloid RW47, m.p. 130-2°,  $[\alpha]_D^{25} +27^\circ$  in  $\text{CHCl}_3$  was shown to possess the molecular formula,  $\text{C}_9\text{H}_{11}\text{ON}$ , from elementary analysis and from the presence of a molecular ion peak at  $m/e$  149 in the MASS spectrum. the IR spectrum showed a hydroxyl band but no carbonyl absorption bands. A sharp strong IR band at  $1600\text{ cm}^{-1}$  and a UV absorption maximum at  $\lambda$  258  $m\mu$  ( $\log \epsilon$  3.65) with a shoulder at  $\lambda$  267  $m\mu$  indicated a single pyridine ring. The 3:4-disubstitution pattern followed from the NMR spectrum. The MASS spectrum provided additional evidence for the presence of a pyridine ring. Thus RW47 was given the structure (42).

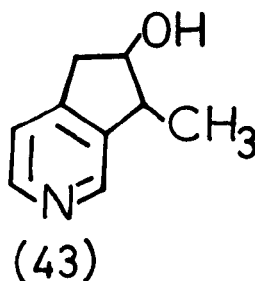


This structure (42) was deduced from spectroscopic data and was preferred because of its relationship to the known cyclopentanoid monoterpene alkaloids ——— actinidine (1), skytanthine (2) and others, having the same carbon skeleton.

Finally, a few months before Ray et al.<sup>24</sup> reported the presence of VENOTERPINE ——— the latest monoterpene alkaloid, in the mature fruits of *Alstonia venenata* R.Br.

Venoterpine,  $C_9H_{11}ON$  ( $M^+$  149), m.p. 128 - 30°,  $\lambda_{\text{max}}^{\text{EtOH}}$  259 m $\mu$  (log  $\epsilon$  3.50) is highly sensitive to light and air and turns purple on keeping. The structural assignment of venoterpine was largely based on its NMR spectrum which permitted the identification of all the eleven protons and suggested that it contained three aromatic protons at  $\delta = 7.15 - 8.36$ ; three benzylic protons at  $\delta = 2.70 - 3.45$ ; three protons due to a benzylic methyl at  $\delta = 1.38$  and two protons due to a  $>CHCH$  system at  $\delta = 4.46 - 4.71$ . The hydroxyl group was also indicated by IR spectrum showing a band at 3160  $\text{cm}^{-1}$ . The strong IR absorption at 1600  $\text{cm}^{-1}$  and particularly the UV absorption maximum of venoterpine which was very similar to actinidine suggested that the aromatic system of the alkaloid was due to a pyridine nucleus. The 3:4-disubstituted

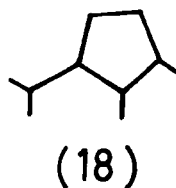
pattern also followed from NMR spectrum and thus venoterpine was thought to have the structure (43).



Although the properties of venoterpine (43) are quite similar to those of the alkaloid RW47 (42), the NMR spectrum of venoterpine was different from that of RW47 in the  $>\text{CHOH}$  region which led to the conclusion that venoterpine (43) is possibly a stereoisomer of RW47 (42). The stereochemistry of venoterpine (43) has not been worked out yet.

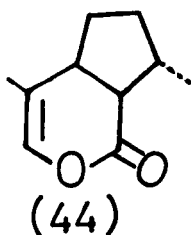
*The chemistry of the compounds related to  
cyclopentanoid monoterpene alkaloids.*

Cyclopentanoid monoterpenes having the nepetane or 1:2-dimethyl-3-isopropyl cyclopentane carbon skeleton (18) have been reported<sup>11,25</sup> from

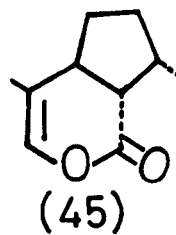


many insect and plant sources.

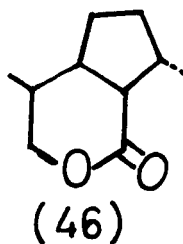
Oil of catnip from the plant *Nepeta cataria* has long been known as an attractant to cats and related species, it is only recently that its chemistry has been elucidated.<sup>11,26</sup> The following nepetalactones have been isolated from the oil and the plant.



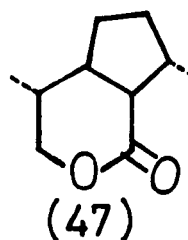
Nepetalactone



Iso-nepetalactone



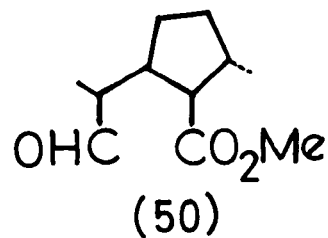
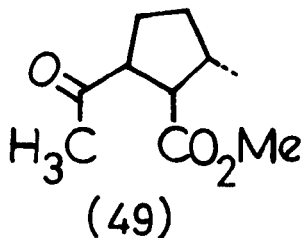
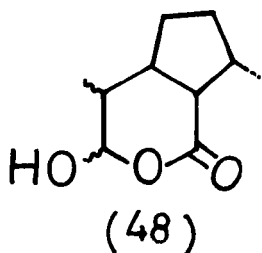
Dihydronepetalactone



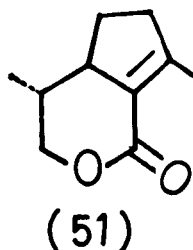
Iso-dihydronepetalactone



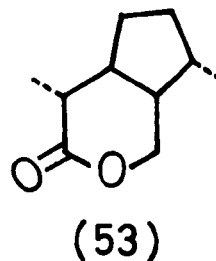
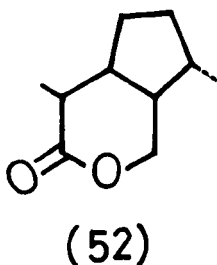
In addition to the nepetalactones (44) - (47), a hydroxylactone (48), methyl nepetonate (49) and an aldehyde ester (50) have also been identified.<sup>26</sup>



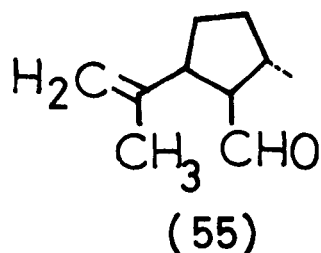
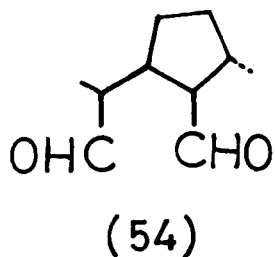
Another nepetalactone ——— Neonepetalactone (51) has been found to be present in the leaves and galls of *Actinidia polygama*.<sup>26</sup>



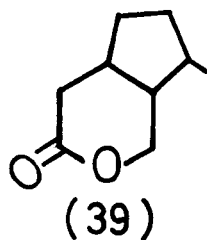
The active principle of the neutral fraction of *Actinidia polygama* ——— another plant liked by Felidae animals, is matatabilactone<sup>11,26,27</sup> ——— a mixture of iridomyrmecin (52) and isoiridomyrmecin (53).



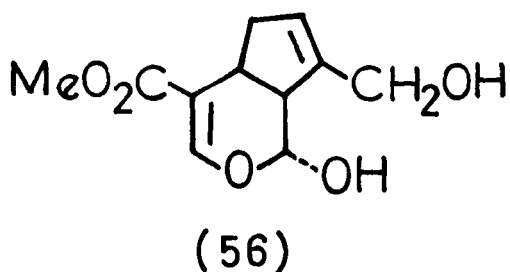
In addition to iridodial<sup>11,25,28</sup> (54) and dolichodial<sup>11,25,28,29</sup> (55), iridomyrmecin (52) and isoiridomyrmecin (53) have also been extracted from the glands of Argentinian and Australian ants.



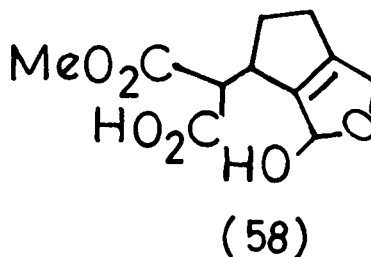
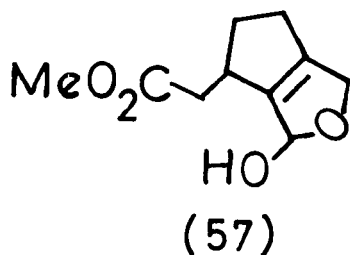
Recently boschnialactone (39) has been isolated<sup>22</sup> from *Boschniakia rossica* Hult, also liked by Felidae animals.



Genipin (56) is the active principle<sup>30</sup> of the plant, *Genipa americana* L.

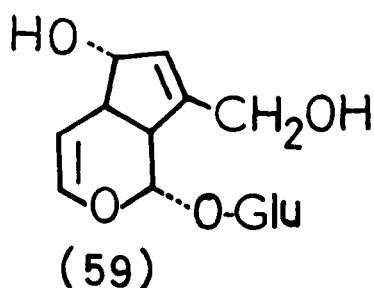


Two antibiotics<sup>31</sup> \_\_\_\_\_ Genipic acid (57) and Genipinic acid (58), have been isolated from the same plant.



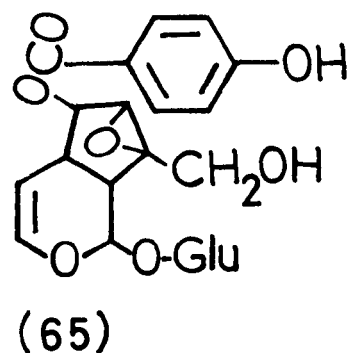
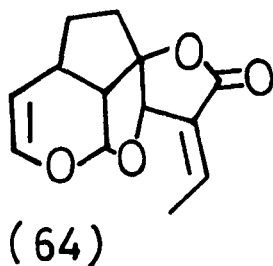
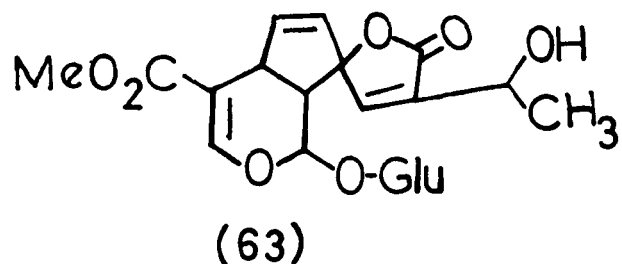
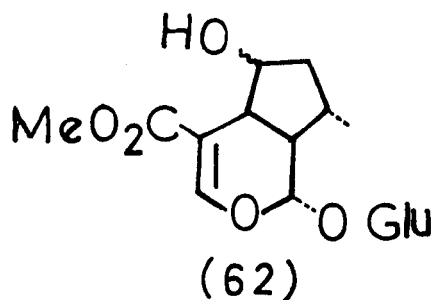
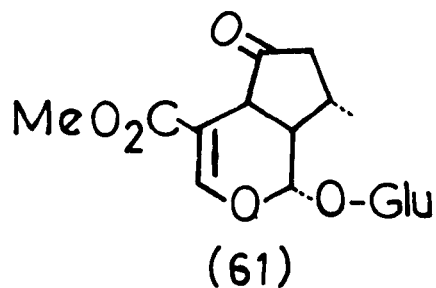
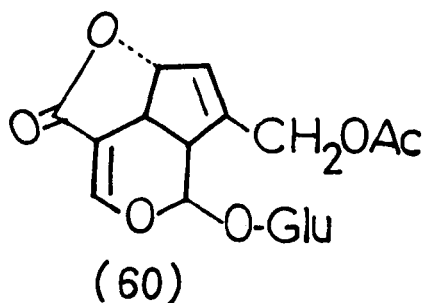
Finally, the cyclopentanoid monoterpene skeleton (18) is also apparent in several glycosides.

Seeds of *Helanthyrum* and of *Rhinanthus* species have long been known as the troublesome contaminants of wheat which cause the resulting bread to be black. This blackening is due to Aucubin<sup>32</sup> (59). Aucubin (59) appears to be the active principle of *Plantago* species and for many years



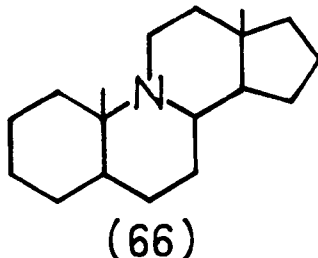
recommended in the French Pharmacopea as a general panacea. It increases the rate of removal of uric acid from the body and the aglucone has antibiotic activity.

Some of the other glycosides containing carbon skeleton (18) are asperuloside<sup>33</sup> (60), verbenalin<sup>34</sup> (61), loganin<sup>35</sup> (62), plumeiride<sup>36</sup> (63), plumericin<sup>37</sup> (64) (not a glycoside), and catalposide<sup>38</sup> (65).



*The chemistry of 9-azasteroids.*

9-Azasteroids have not been found in nature and are thus unrelated to cyclopentanoid monoterpene alkaloids. They possess the skeleton (66).

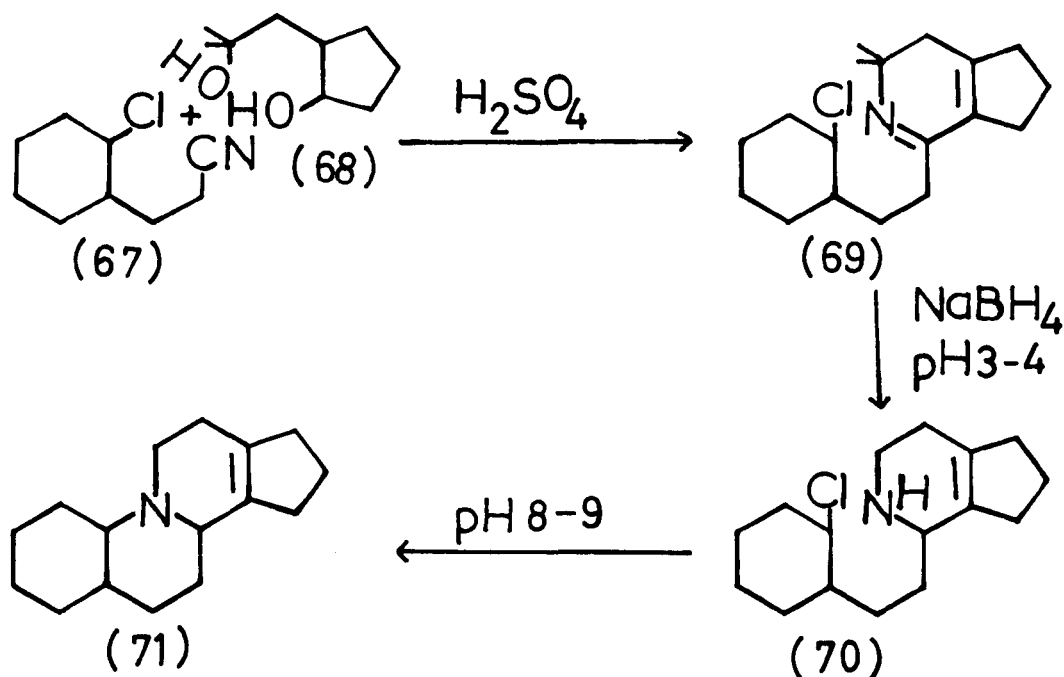


However, the C/D ring system in a 9-azasteroid is essentially the same as those of the monoterpene alkaloids.

The modification of naturally occurring steroids causes enhancement or suppression of certain facets of their activity. The activity of steroid hormones is, in general, specifically related to their structure and it has been found that only a limited number of structural variations are possible with retention of biological activity.<sup>39</sup> Replacement of trigonal  $sp^2$  carbon by trigonal nitrogen, or of tetrahedral  $sp^3$  carbon by tetrahedral positively charged nitrogen,<sup>40</sup> and expansion of one of the rings from 6- to 7-membered,<sup>41</sup> produce little change in overall size or configuration. Hence synthetic azasteroids may be of therapeutic value.

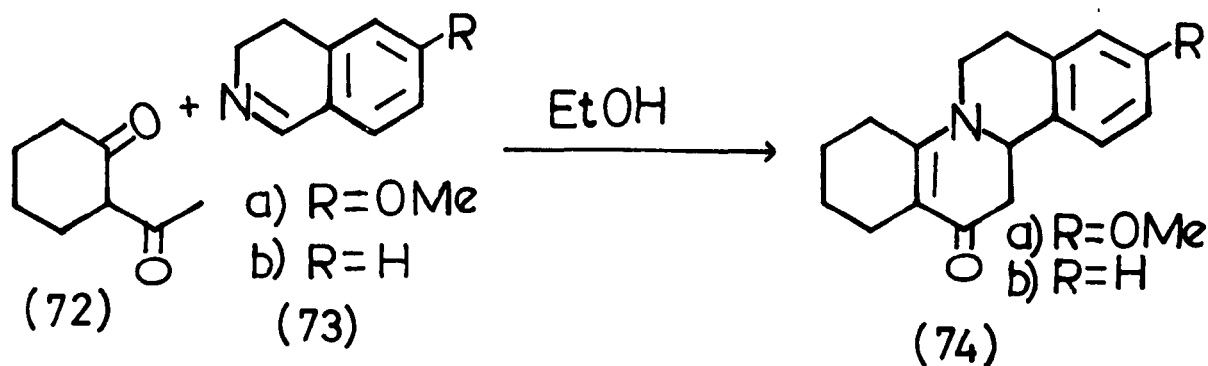
Although a 9-azasteroid has not yet been prepared, some approaches have been reported.

The first one of Meyers et al.<sup>42</sup> is outlined below:-

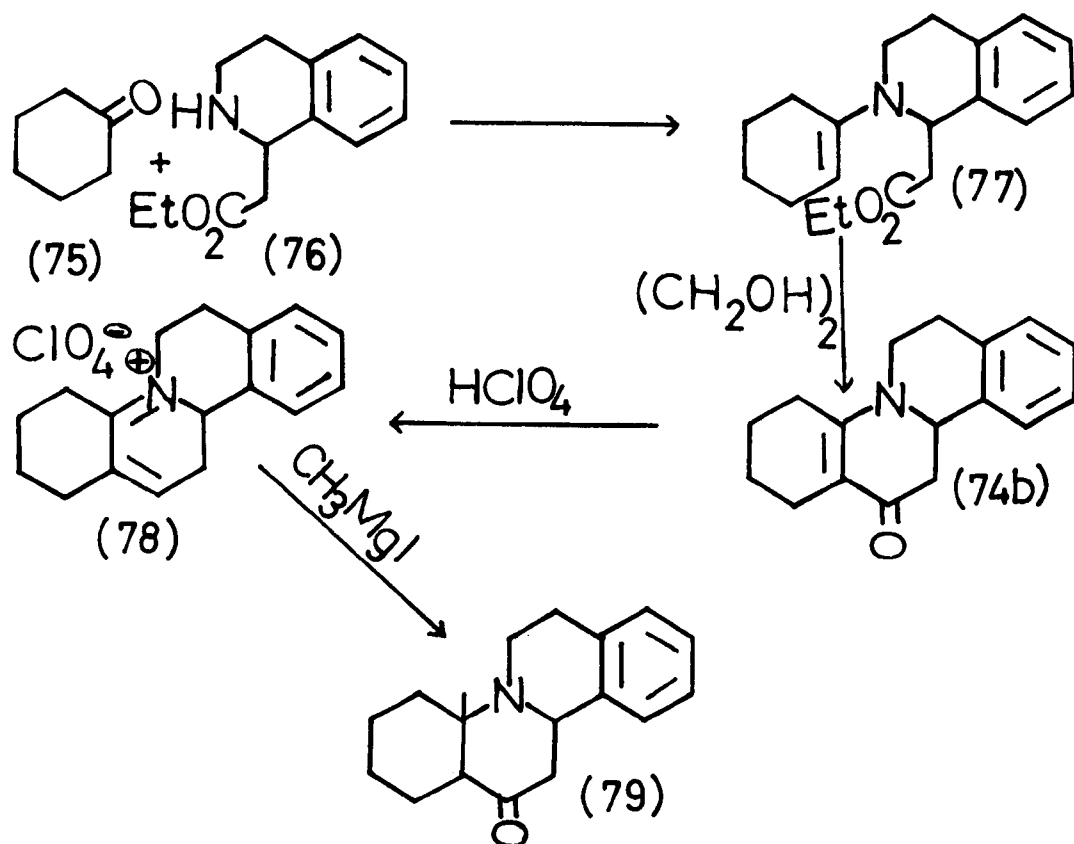


One of the features of this synthesis is that isolation of the dihydropyridine (69) and tetrahydropyridine (70) is unnecessary, suitable conditions for the reduction and subsequent cyclisation being achieved by dilution with water and adjustment of the pH.

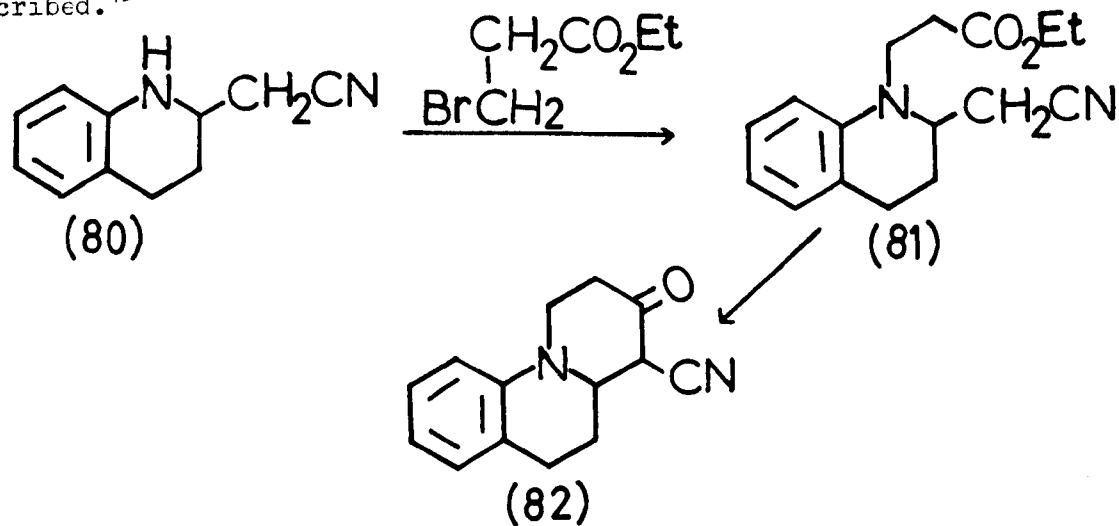
D-Homo-9-azasteroids have been synthesised by two methods. In one method, M. von Strandtmann et al.<sup>43</sup> prepared compounds (74, a and b) by condensation of the corresponding 3:4-dihydroisoquinoline (73, a and b) with 2-acetyl cyclohexanone (72).



The compound (74b) has also been prepared by Meyers et al.<sup>44</sup> and converted into the methylated derivative (79) by reaction of its perchlorate salt with methyl magnesium iodide.

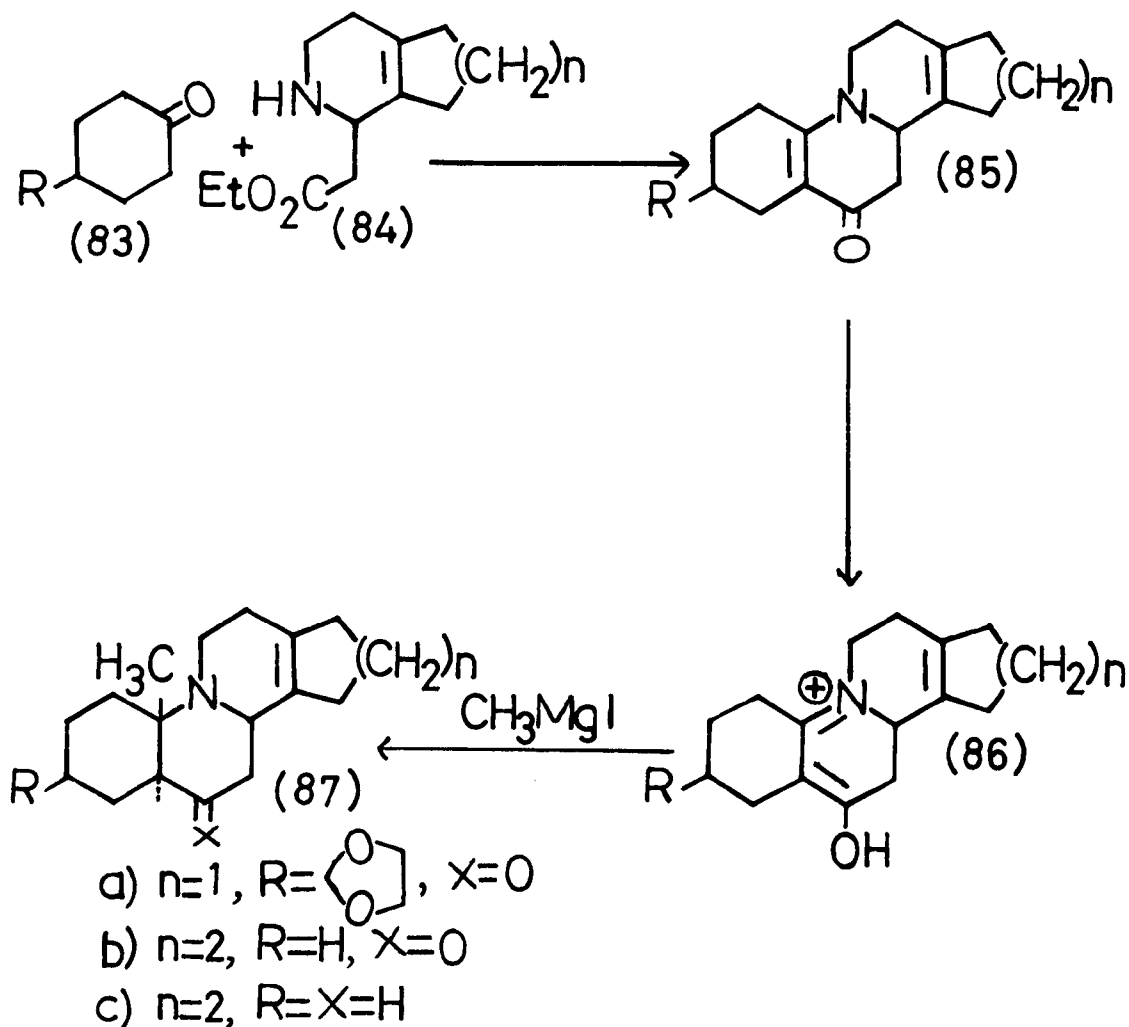


In another attempt, a synthesis of the compound (82) has been described.<sup>45</sup>





Finally the syntheses of an 18-nor-9-azaandrost- $\Delta^{13(14)}$ -ene-6-one (87a) and related D-homo-derivatives (87, b and c) have been reported.<sup>46</sup>



Treatment of the piperidine esters (84, a and b) with the monoketal of 1:4-cyclohexane dione (83a) in refluxing toluene produced the tetracyclic systems (85, a and b) respectively. In a similar fashion, the compound (84b) and cyclohexanone (83b) yielded the 3-nor-derivative (85c). Introduction of the C-10 methyl was accomplished smoothly when the perchlorate salt (86b) was reacted with excess methyl magnesium

iodide in hexane affording (87).

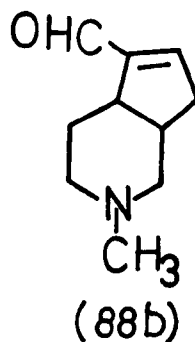
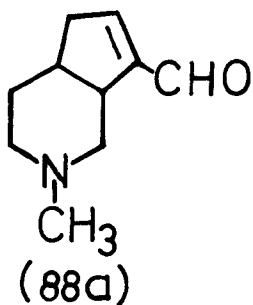
Angular methylation of (85a) or (85b) could not be accomplished via the perchlorate salts since the ketal linkage at C-3 readily cleaved during salt formation. Reaction of (85a) with acetyl chloride produced the C-acetyl derivative (86a) which was used in situ in the reaction with methyl magnesium iodide forming (87a).

## DISCUSSION

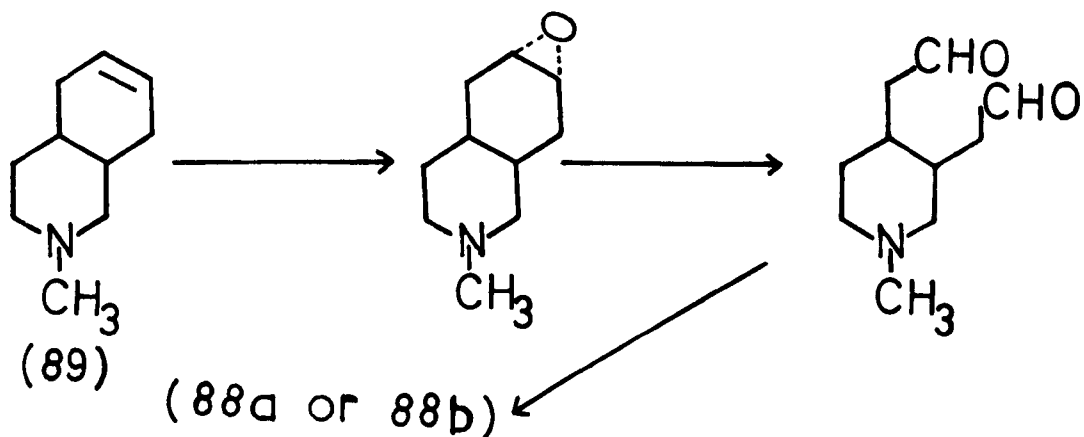
*P A R T      I*

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Initial experiments were directed towards the syntheses of the compounds (88 a and b) which are closely related to Tecoma stans alkaloids.

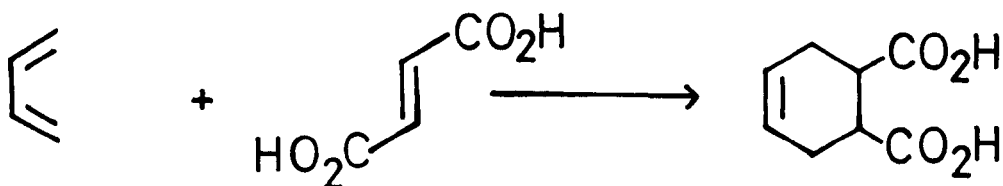


These compounds could be made from N-methyl-hexahydroisoquinoline (89) through the following series of reactions



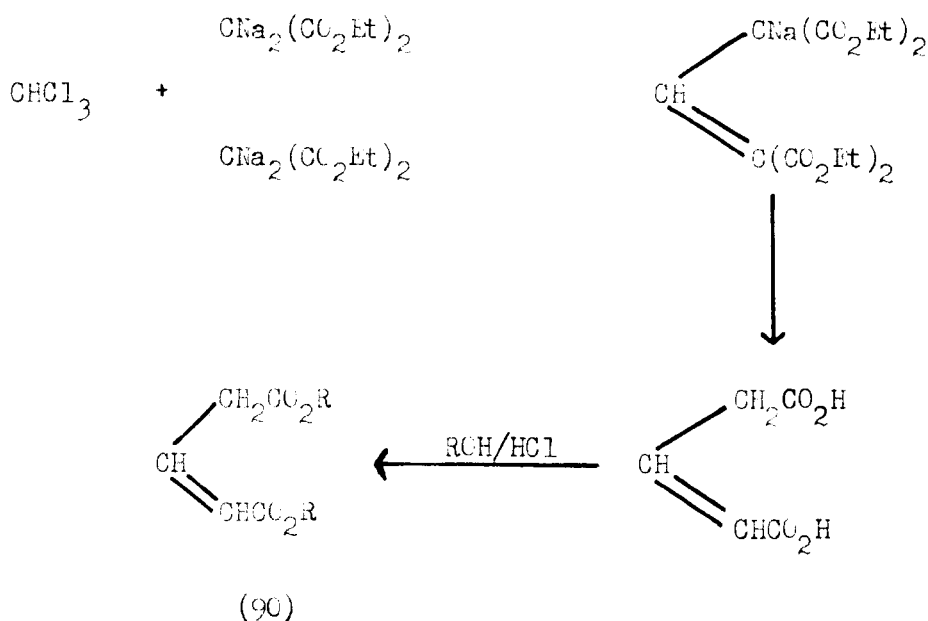
For the preparation of hexahydroisoquinolines a number of procedures are available and use was made of the Diels-Alder reaction.<sup>47</sup>

The Diels-Alder reaction is the addition of a compound containing a double or triple bond, which is usually activated by additional unsaturation in the  $\alpha:\beta$ -position and is known as the dienophile, to the 1:4-positions of a conjugated diene system resulting in the formation of a six-membered hydroaromatic ring. The addition of a dienophile to a diene is a purely cis-addition and the relative positions of substituents in dienophile are retained in the adduct. For example tetrahydrophthalic acid<sup>48</sup> can be obtained by the addition of fumaric acid to butadiene.



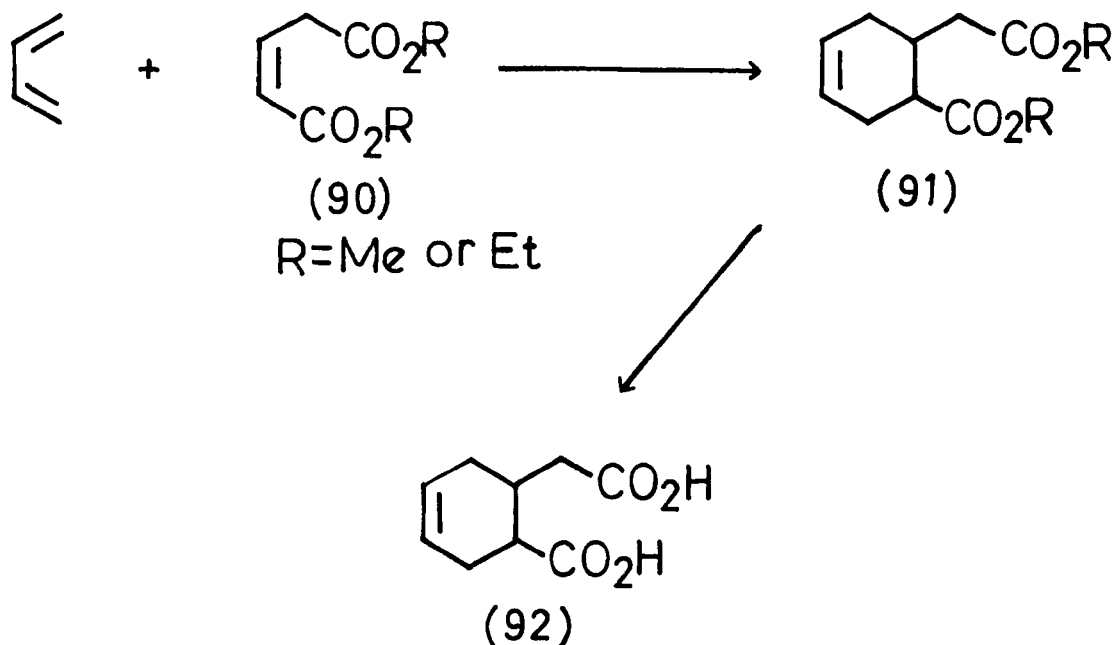
The tetrahydrohomophthalic acids required for the preparation of N-methyl-hexahydroisoquinoline (89) were obtained by two different procedures.

In one method,<sup>49</sup> dimethyl and diethyl esters of glutaric acid (90) were made<sup>50</sup> from the sodium salt of diethylmalonate/absolute ethanol and chloroform.

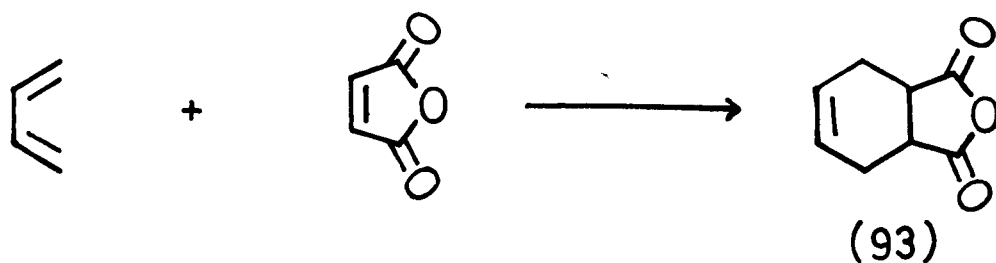


R = Me or Et

These esters of glutaconic acid (90) when heated with butadiene in an autoclave in the presence of a catalytic amount of picric acid yielded the corresponding esters of tetrahydrohomophthalic acid (91) which on hydrolysis with 20% sodium hydroxide, gave tetrahydrohomophthalic acid (92).



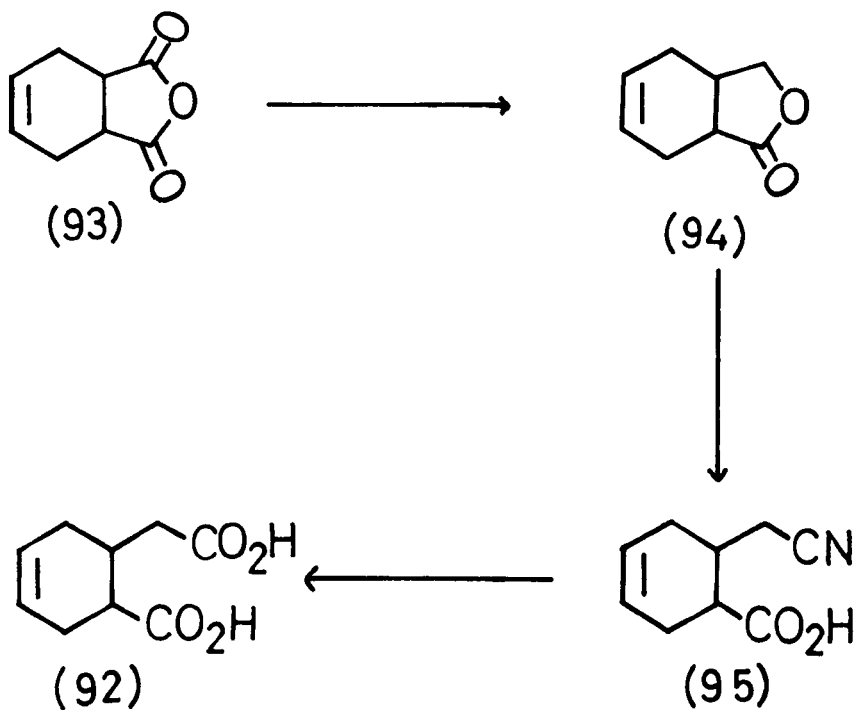
In the other method,<sup>51</sup> butadiene was introduced into a solution of maleic anhydride in dry benzene<sup>52</sup> to form tetrahydrophthalic anhydride (93).



Tetrahydrophthalic anhydride (93) when treated with sodium or potassium borohydride in dry DMF gave the cis  $\gamma$ -lactone (94), and this with sodium cyanide in DMSO formed a mixture of cis and trans nitrile acids (95) which on hydrolysis with sodium hydroxide gave a mixture of

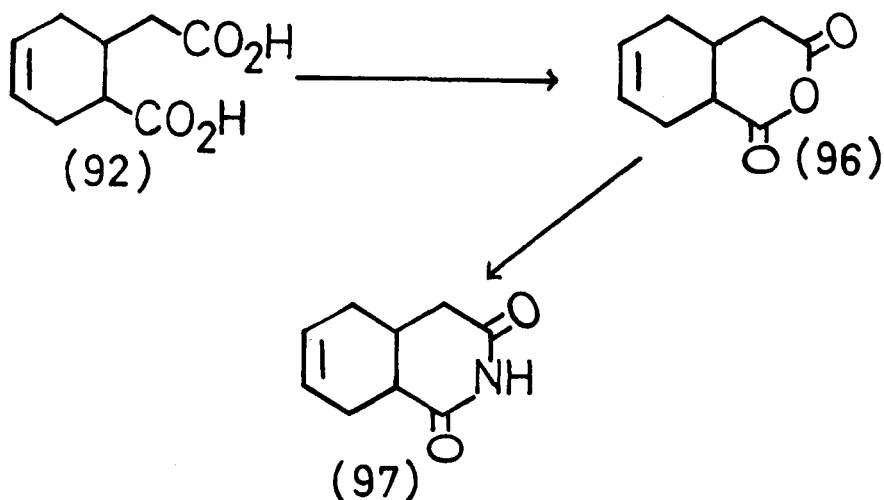


cis- and trans-tetrahydrohomophthalic acids (92). The cis isomer was

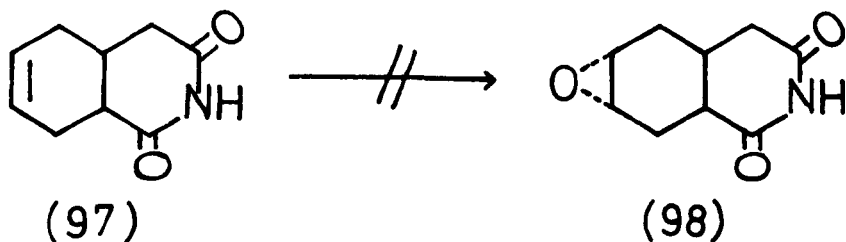


separated by recrystallisation from water and converted into the trans form through the anhydride.

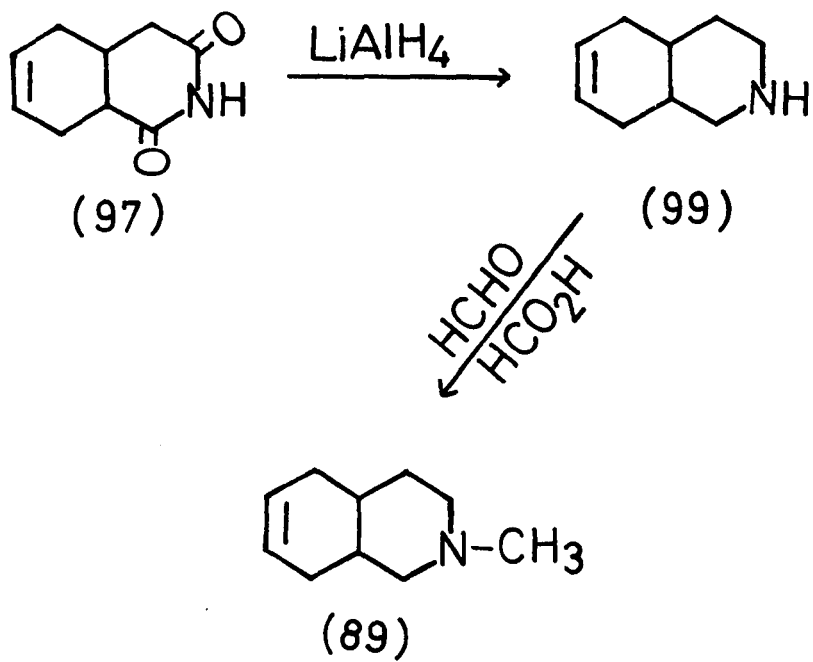
The tetrahydrohomophthalic acid (92) with acetyl chloride in benzene gave the trans anhydride (96) which on treatment with ammonia or urea furnished the imide (97).



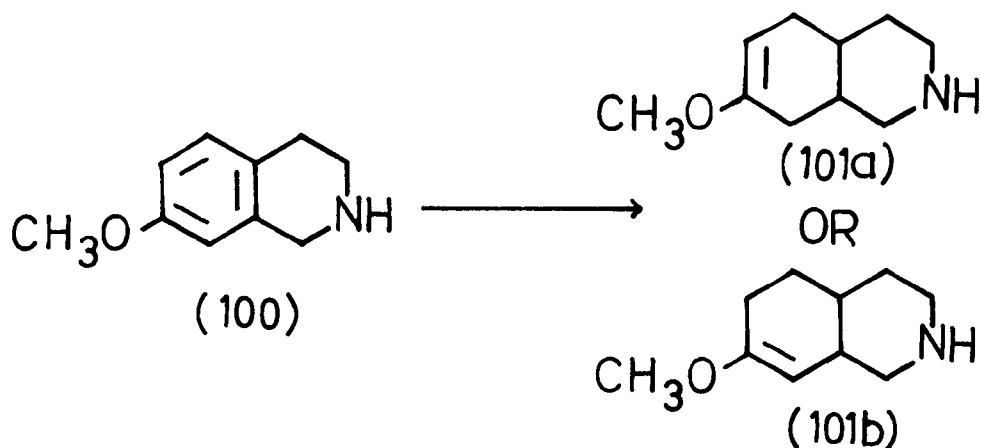
A variety of conditions were tried for the conversion<sup>53</sup> of imide (97) into epoxide (98) using monoperphthalic acid<sup>54</sup> but without success.



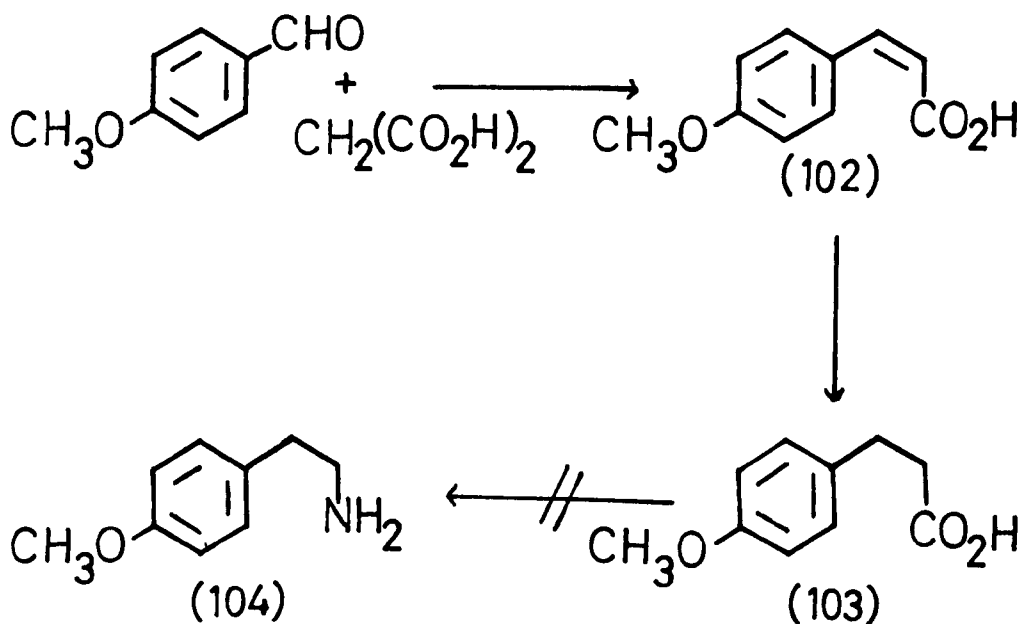
The yield of the trans-tetrahydrohomophthalimide (97) was so low that it was not worthwhile to continue this approach although the compound (97) could be reduced<sup>49,51</sup> to hexahydroisoquinoline (99) which would be converted easily to N-methyl-hexahydroisoquinoline (89).



later, the synthesis of 8-methoxy-tetrahydroisoquinoline (100) was attempted. This compound (100), it was thought, would give through Birch reduction<sup>56</sup> 8-methoxy-hexahydroisoquinoline (101 a or b).

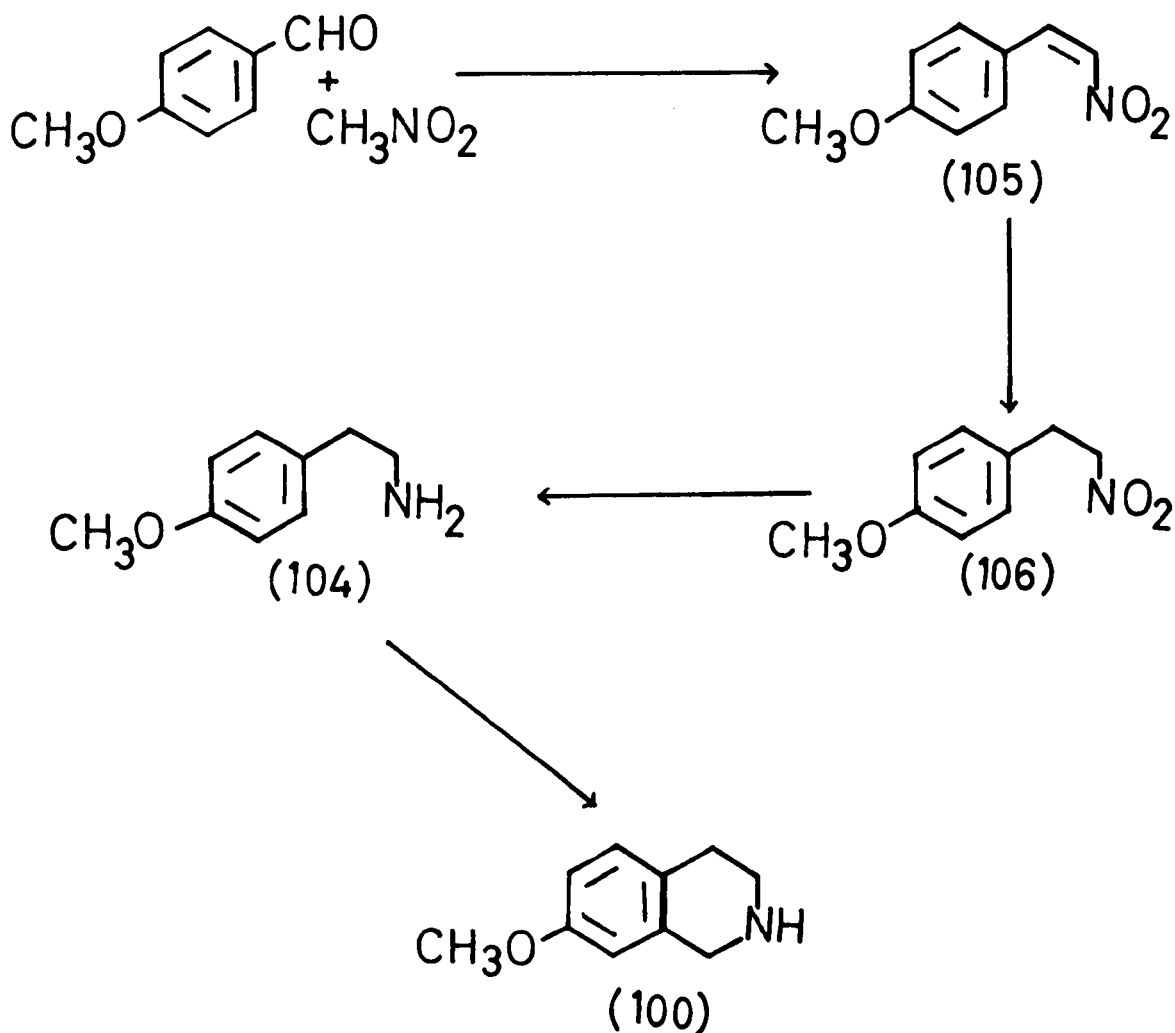


When anisaldehyde was condensed with malonic acid in pyridine containing a catalytic amount of piperidine, the reaction mixture yielded<sup>57</sup> 4-methoxy-cinnamic acid (102) or acidification.



4-methoxy-cinnamic acid (102) on reduction<sup>58</sup> with hydrogen and Adams' catalyst in ethanol gave  $\beta$ -(p-methoxy-phenyl)-propionic acid (103) in almost quantitative yield. However, several attempts to convert  $\beta$ -(p-methoxy-phenyl)propionic acid (103) through Schmidt reaction<sup>59</sup> into  $\beta$ -(p-methoxy-phenyl)ethyl amine (104) failed.

On the other hand, when anisaldehyde and nitromethane were condensed<sup>60</sup> in absolute ethanol at room temperature, in the presence of a catalytic amount of methylamine hydrochloride and sodium carbonate (anhydrous), gave, after 10 days, the nitrostyrene (105).

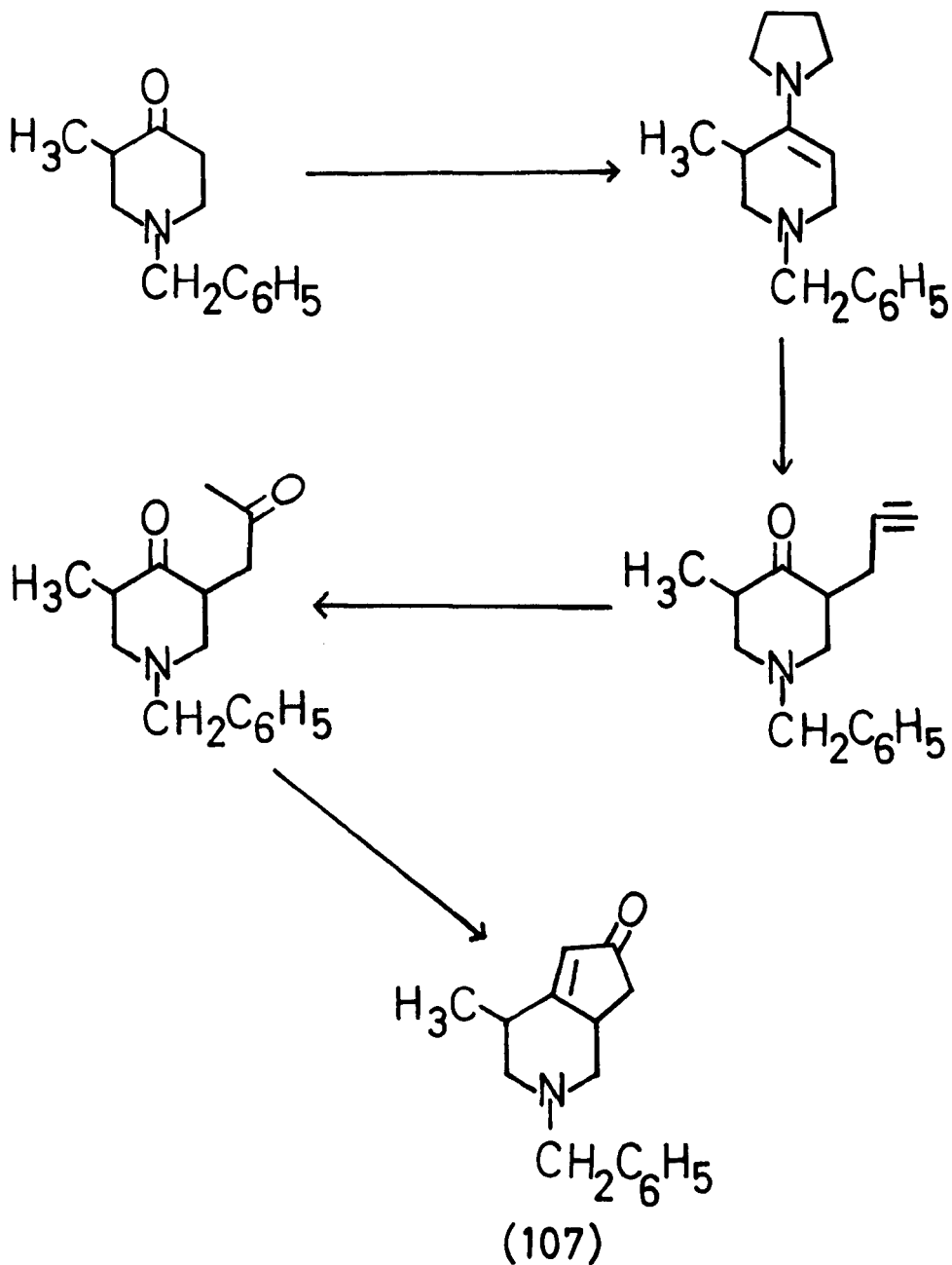


When the nitrostyrene (105) was reduced with hydrogen and Adams' catalyst, only the double bond was reduced and the nitro group was unaffected. However, the nitro group of  $\beta$ -(p-methoxy-phenyl)nitroethane (106) was reduced<sup>61</sup> with lithium aluminium hydride to give the  $\beta$ -(p-methoxy-phenyl)ethylamine (104).

*P A R T   I I*

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In the meantime, Dr. J. D. Baty<sup>62</sup> in this laboratory successfully synthesised 2-benzyl-1:2:3:4:7:7a-hexahydro-4-methyl-6-H-2-pyridin-2-one (107).

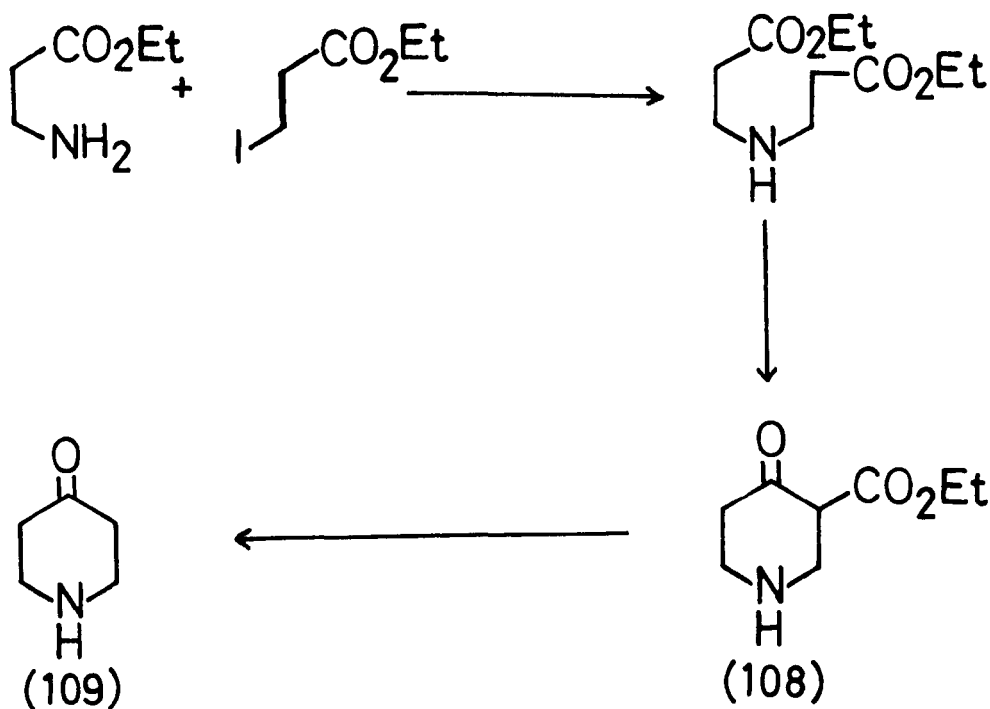




However, this compound (107) which has the same structure as tecomanine ( 3 ) except for the presence of an N-benzyl group instead of an N-methyl group and for the lack of a third methyl group at 7-position, could not be reduced and converted to the corresponding N-methyl compound since the reduction of the double bond would also occur. So it was decided to use the same sequence of reactions for the preparation of the corresponding N-methyl compound.

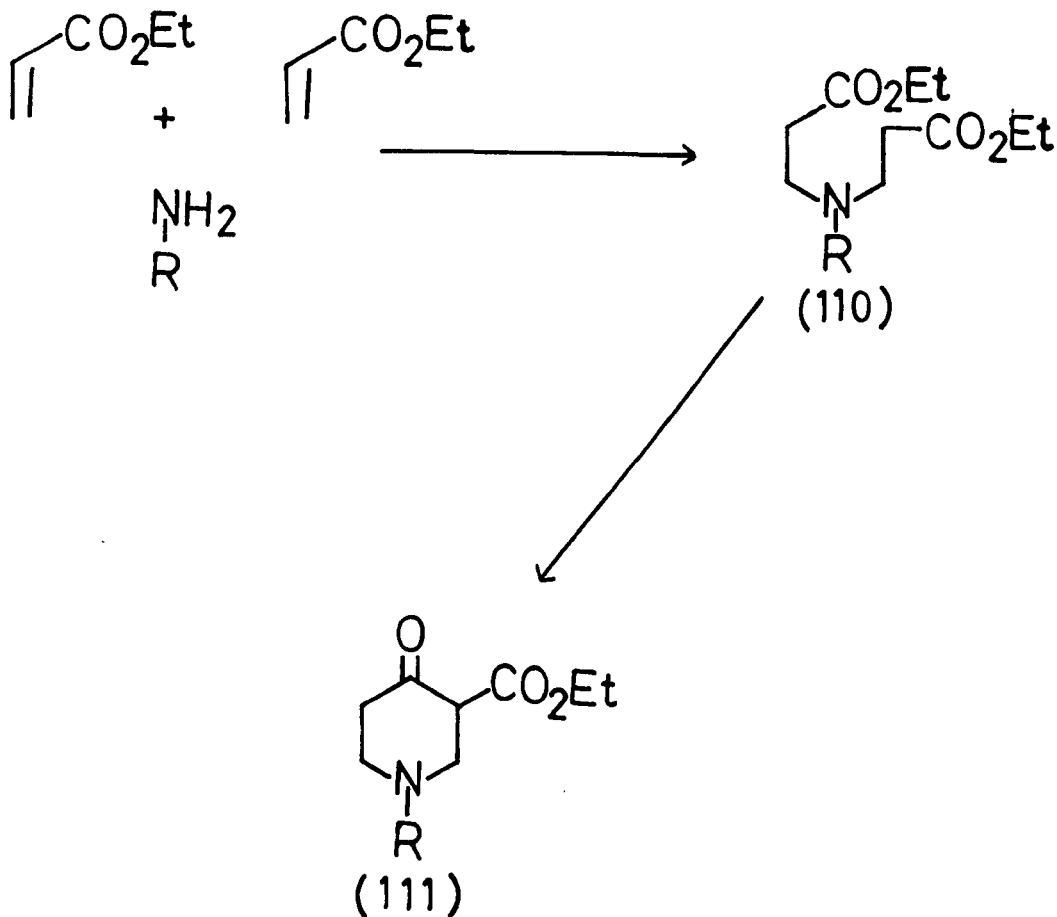
SYNTHESIS OF 1:3-DIMETHYL-4-PIPERIDONE

4-Piperidones, in general, are of interest because of their use as intermediates in the production of pharmacologically active materials,<sup>63</sup> and one of the most important piperidone syntheses involves the Dieckmann condensation of suitable dicarboxylic esters or nitriles, in which the ring closure is completed between the carbon atoms in the  $\beta$ - and  $\gamma$ -positions. The first of such ring closures was reported by Ruzicka and Fournesir<sup>64</sup> who first sought to prepare 4-piperidone from 4-pyridone by catalytic hydrogenation but obtained 4-piperidinol. They treated ethyl  $\beta$ -iodopropionate with ethyl  $\beta$ -amino-propionate to obtain di-( $\beta$ -carboethoxy-ethyl)amine. On treatment with sodium, this

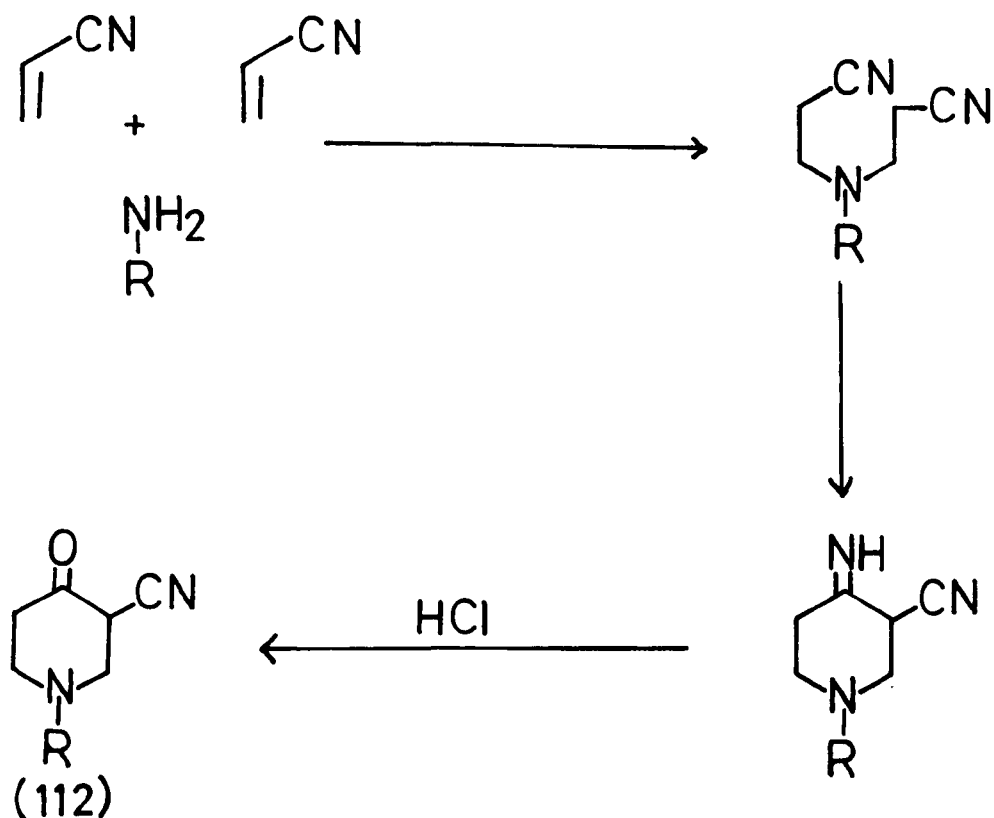


gave a poor yield of 3-carboethoxy-4-piperidone (108). The product (108) was hydrolysed and decarboxylated to 4-piperidone (109).

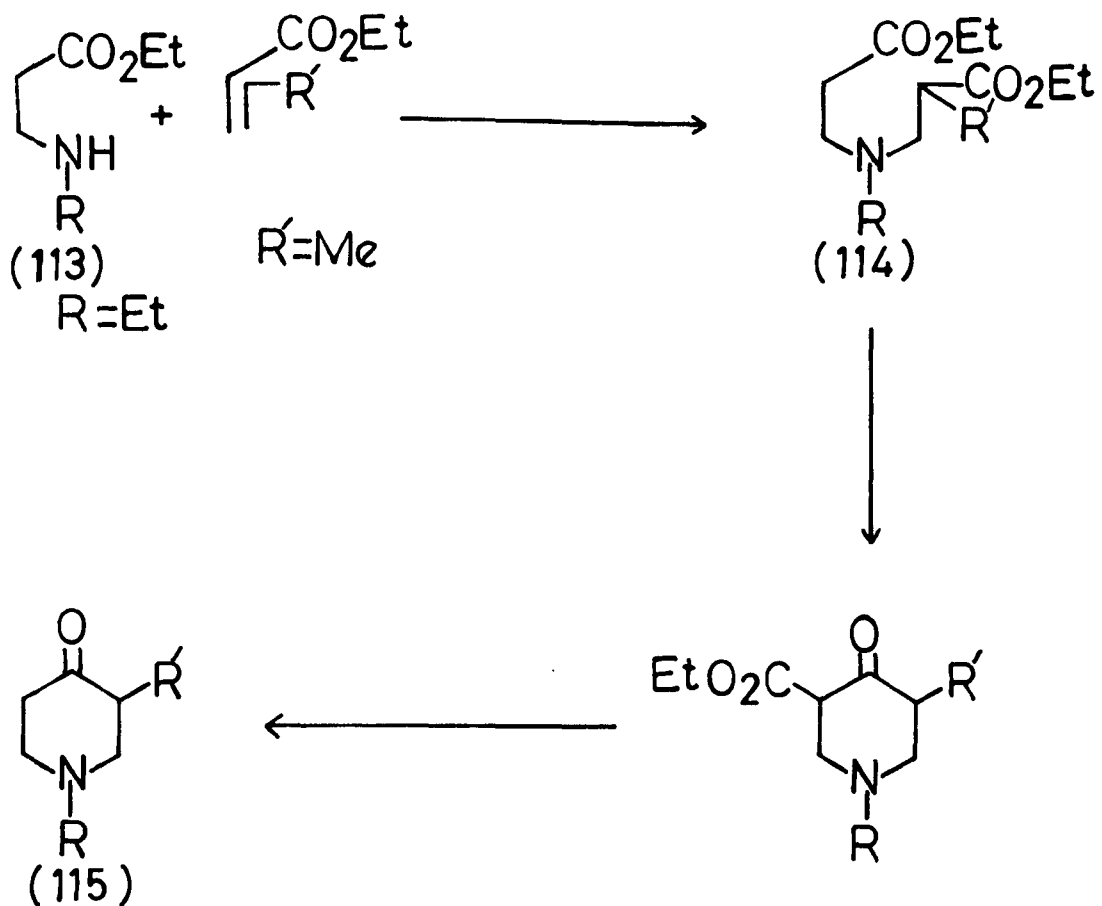
Further study of the Dieckmann reaction resulted in a slightly better procedure but still with low yields.<sup>65</sup> However, higher yields have been reported when a tertiary amine is employed.<sup>66-75</sup> In addition, the starting esters (110) were made in excellent yields by addition of primary amines to ethyl acrylate.<sup>70</sup>



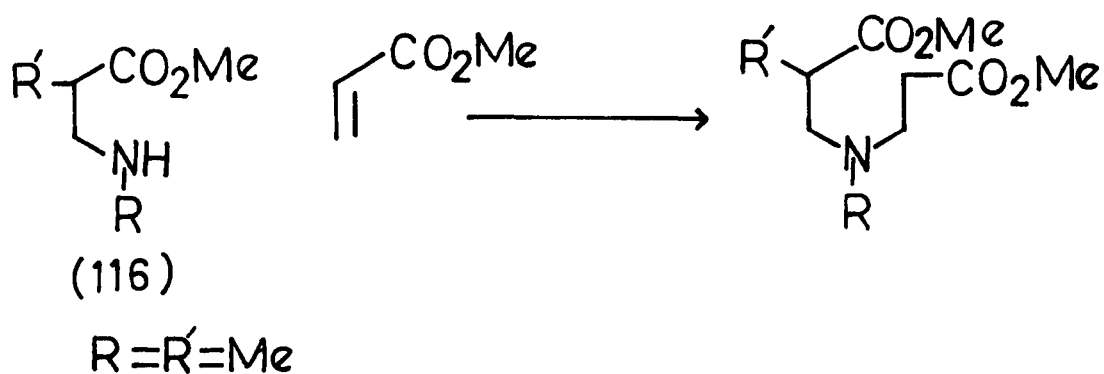
This reaction has been successfully conducted with compounds in which R was an alkyl group from methyl to pentyl, as well as phenyl, benzyl,  $\beta$ -phenethyl and benzoyl. The reaction was equally successful when acrylonitrile was substituted for ethyl acrylate, the product being a 3-cyanopiperidone<sup>76-79</sup> (112).



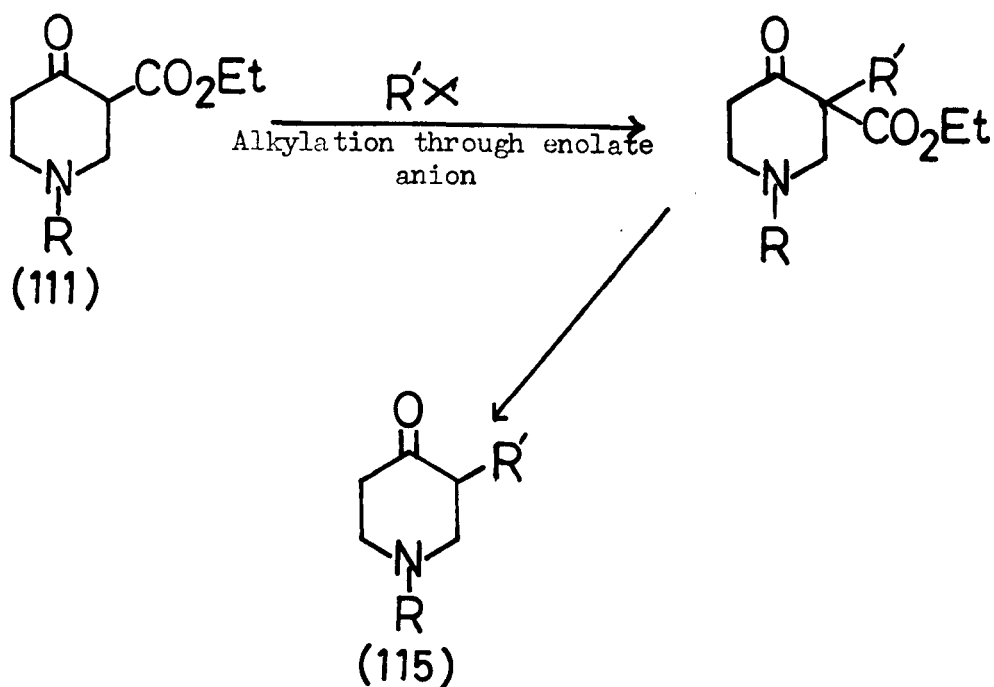
3-Alkyl-4-piperidones (115) were obtained by the addition of 3-carboethoxy-alkyl-amine (113) to ethyl 2-alkyl-acrylate.<sup>8C</sup>



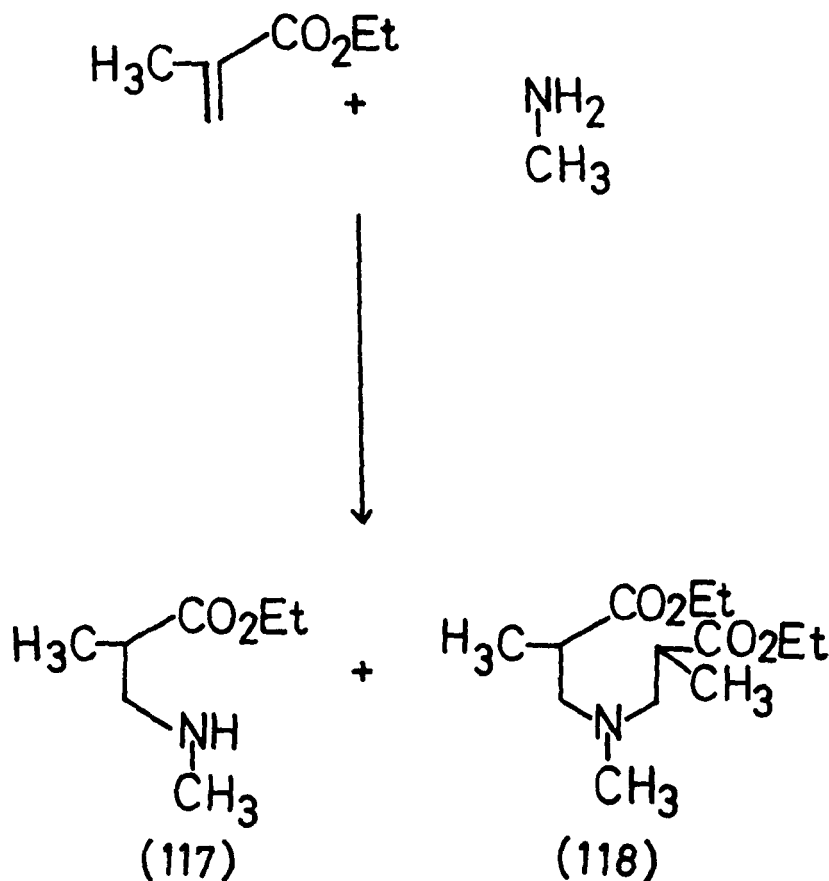
However, better yields of the compounds of the type (114) were obtained when methyl( $\beta$ -carbomethoxy- $\beta$ -alkyl-ethyl)amine (116) was added to methyl acrylate.<sup>71</sup>



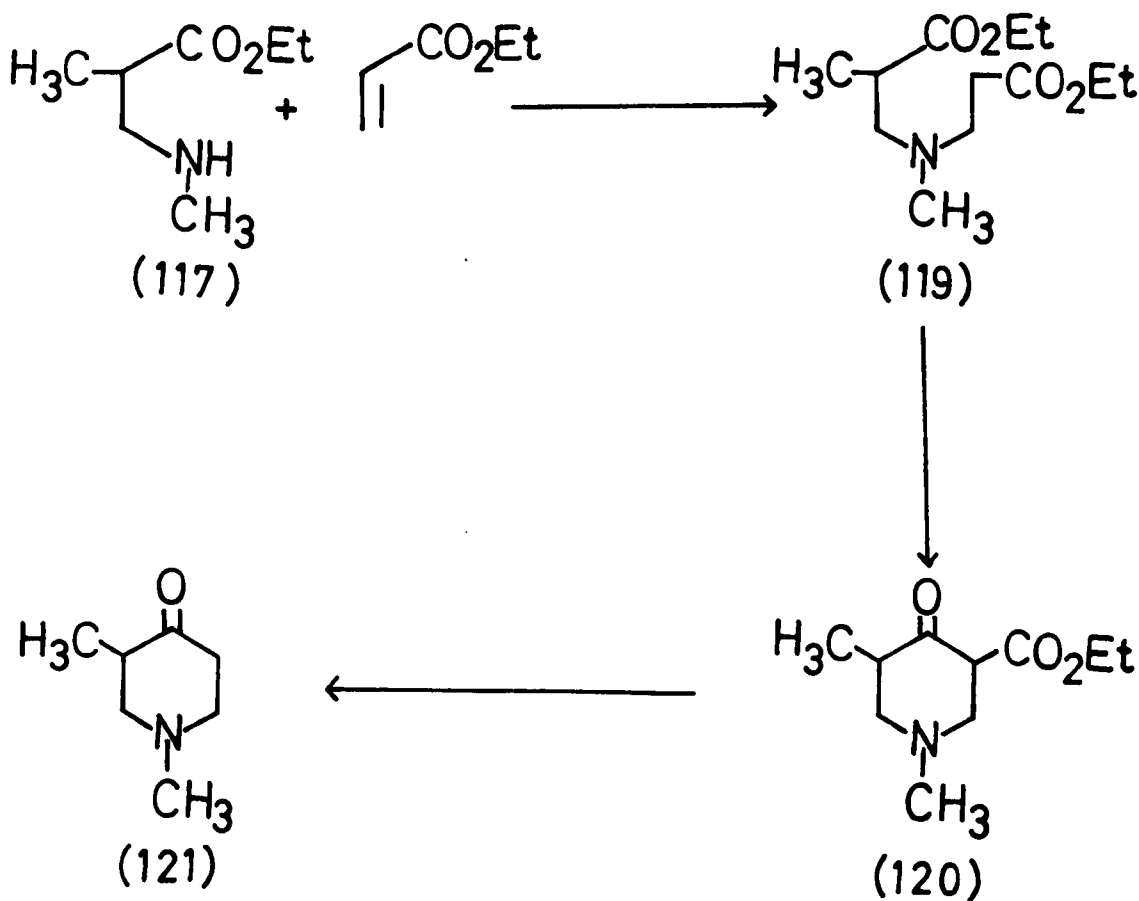
Compounds of the type (115) were also made by the alkylation of the keto ester (111) using alkyl halides.<sup>63,72</sup>



1:3-Dimethyl-4-piperidone required for this synthesis was known<sup>71</sup> and made by starting with methyl methacrylate and methylamine in methanol. However, the yield of methyl( $\beta$ -carboethoxy-n-propyl)amine (117) was improved when a mixture of ethyl methacrylate (1 mole), methylamine in ethanol (33%; 1.25 mole) and absolute ethanol was allowed to stand at room temperature for 9 or 10 days. Fractionation of the mixture, on the 9th or 10th day, afforded 80-85% of methyl( $\beta$ -carboethoxy-n-propyl)amine (117) together with a small quantity of the higher boiling di-( $\beta$ -carboethoxy-n-propyl)methyl amine (118).



Methyl( $\beta$ -carboethoxy-n-propyl)amine (117), when mixed with a slight excess of ethyl acrylate and allowed to stand at room temperature for 4 days, could not give methyl( $\beta$ -carboethoxy-ethyl)( $\beta$ -carboethoxy-n-propyl)amine (119) in more than 70% yield. But when the mixture of methyl( $\beta$ -carboethoxy-n-propyl)amine (117) and ethyl acrylate was allowed to stand at room temperature for 4 hours, warmed for another 4 hours, with occasional shaking and then heated under reflux for 15 hours, gave on distillation 90-95% of methyl( $\beta$ -carboethoxy-ethyl)( $\beta$ -carboethoxy-n-propyl)amine (119).





Cyclisation of methyl( $\beta$ -carboethoxy-ethyl)( $\beta$ -carboethoxy-n-propyl)-amine (119) was performed under a variety of reaction conditions using sodium hydride in benzene, sodium hydride in toluene and sodium ethoxide in xylene, in an atmosphere of nitrogen and it was found that a yield of 80% or over of the distilled 1:5-dimethyl-3-carboethoxy-4-piperidone (120) was obtained when sodium hydride in benzene was used. The reaction was quite simple and ethanol formed during the reaction was not distilled out of the reaction mixture.

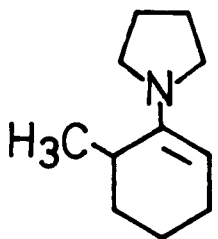
1:5-Dimethyl-3-carboethoxy-4-piperidone (120) was then heated under reflux with 30% hydrochloric acid until the solution gave no violet coloration with ferric chloride, 4 to 5 hours were usually required for the complete decarboxylation. The cold reaction mixture on basification, extraction with ether, evaporation of the solvent and distillation of the residue, furnished 1:3-dimethyl-4-piperidone (121) in 80% yield or over.

SYNTHESIS OF 1:5-DIMETHYL-3-ACETONYL-4-PIPERIDONE

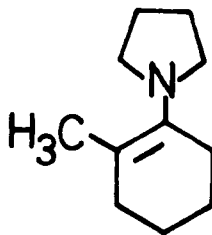
a) BY ALKYLATION OF THE ENAMINE OF 1:3-DIMETHYL-4-PIPERIDONE

It has been found quite difficult to alkylate the enamines of basic ketones with reactive halides, because quaternisation of the nitrogen in the piperidone is a competing reaction, though under the correct conditions, the markedly nucleophilic character of the enamine could allow the alkylation to proceed at the desired position  $\alpha$ - to the carbonyl group.

The study of the structure of the enamine from 2-substituted cyclohexanones <sup>81</sup>, revealed that alkylation of such an enamine occurred at position-6, implying that the direction of the enamine alkylation was towards this unsubstituted position of the ketone. It has been shown that the pyrrolidine enamine of 2-methyl-cyclohexanone is composed of 90% of the compound (122a) and 10% of its isomer (122b).



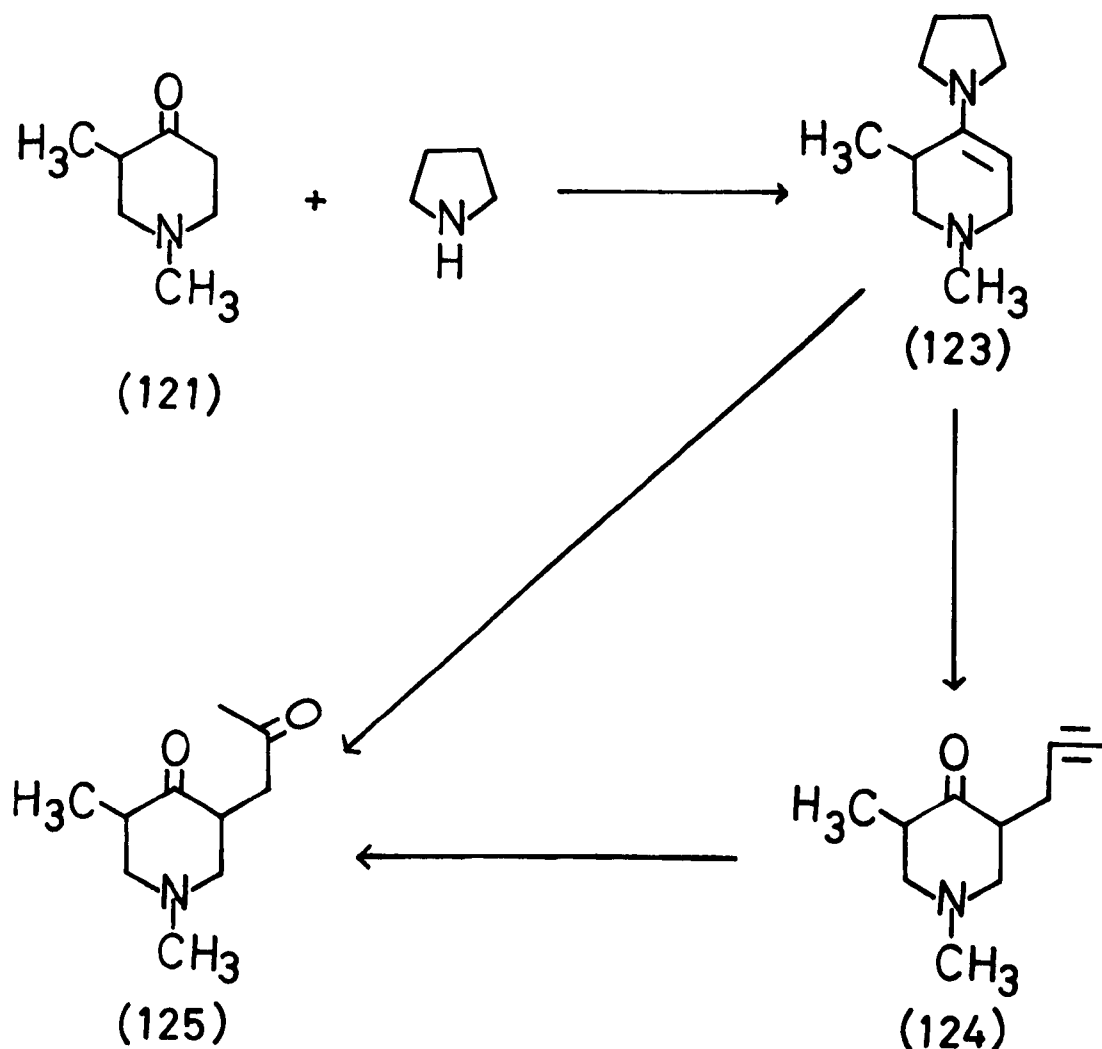
(122)  
a



(122)  
b

However, with diethylamine as the base, the proportion of the isomer corresponding to (122a) is only 25%, while 75% of the enamine exists in the more highly substituted form (122b).

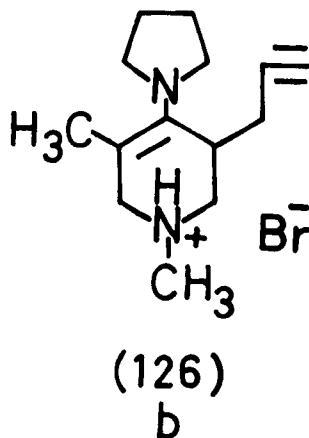
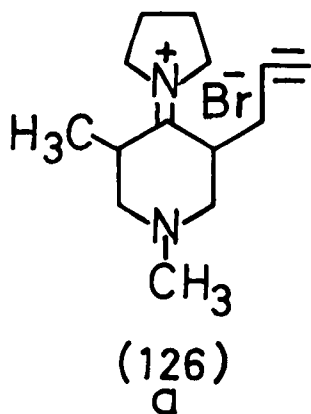
The pyrrolidine enamine (123) of 1:3-dimethyl-4-piperidone was prepared in 85% yield by the standard procedure.<sup>82</sup> The use of a catalytic amount of p-toluene sulphonic acid reduced the time required for complete reaction to 5 hours. The enamine (123) was distilled and its NMR spectrum performed immediately on a sample of the distillate. It showed a single vinyl hydrogen as a triplet centred at 4.28 p.p.m. ( $J = 3$  c.p.s.). The signal due to the methyl resonance appeared as a doublet centred at 1.23 p.p.m., the shift to a lower field being due to the effect of the allylic double bond. Comparison of the integrated proton signals of the vinyl and methyl hydrogens confirmed that the enamine had formed exclusively in the required direction, i.e. away from the 3-methyl group.



The reaction of the enamine (123) with propargyl bromide was performed in dry benzene solution under nitrogen. This solvent system had been used for the reaction of propargyl bromide with the enamine of 1-benzyl-3-methyl-4-piperidone.<sup>62</sup>

The freshly distilled enamine (123), a colourless oil, was dissolved in dry benzene and an equimolar amount of propargyl bromide was added during 10 minutes with stirring at room temperature. A mildly

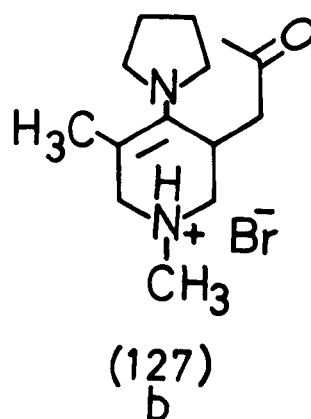
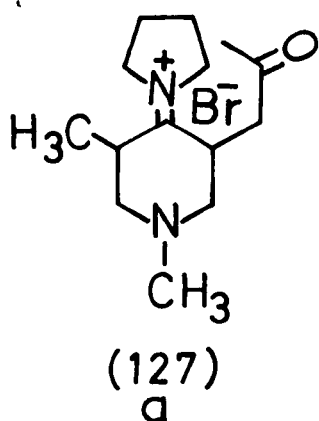
exothermic reaction occurred and an orange waxy solid began to appear. This solid separating out from the reaction mixture must presumably be the hydrobromide of the alkylated enamine (126a) or (126b).



The stirring was continued for 45 hours. The enamine complex was decomposed by stirring with water for 30 minutes at room temperature. Extraction of the product and chromatography on Woelm alumina gave a 60% yield of 1:3-dimethyl-5-(prop-2-ynyl)-4-piperidone (124) as a pale yellow oil. The IR spectrum (film) showed a band at 3300 cm.<sup>-1</sup> (C≡CH), 1705-1712 cm.<sup>-1</sup> (C=O). The NMR spectrum (CDCl<sub>3</sub>) showed the methylene group as a sharp doublet centred at 3.37 p.p.m. The acetylenic hydrogen was not clearly resolved. The doublet due to the methyl group was centred at 1.09 p.p.m. and the N-methyl singlet appeared at 2.4 p.p.m.

The hydration of this acetylenic compound (124) was performed by the method of Jones et al.<sup>83</sup> with the boron-trifluoride-mercuric oxide catalyst in methanol. The methanol solution was concentrated, filtered from the inorganic material and heated for 20 minutes at approximately 50° with a 10% aqueous solution of sulphuric acid. Basification with dilute ammonia and chloroform extraction gave 3-acetyl-1:5-dimethyl-4-piperidone (125) in 50% yield. This compound like the acetylenic precursor was purified by chromatography on alumina.

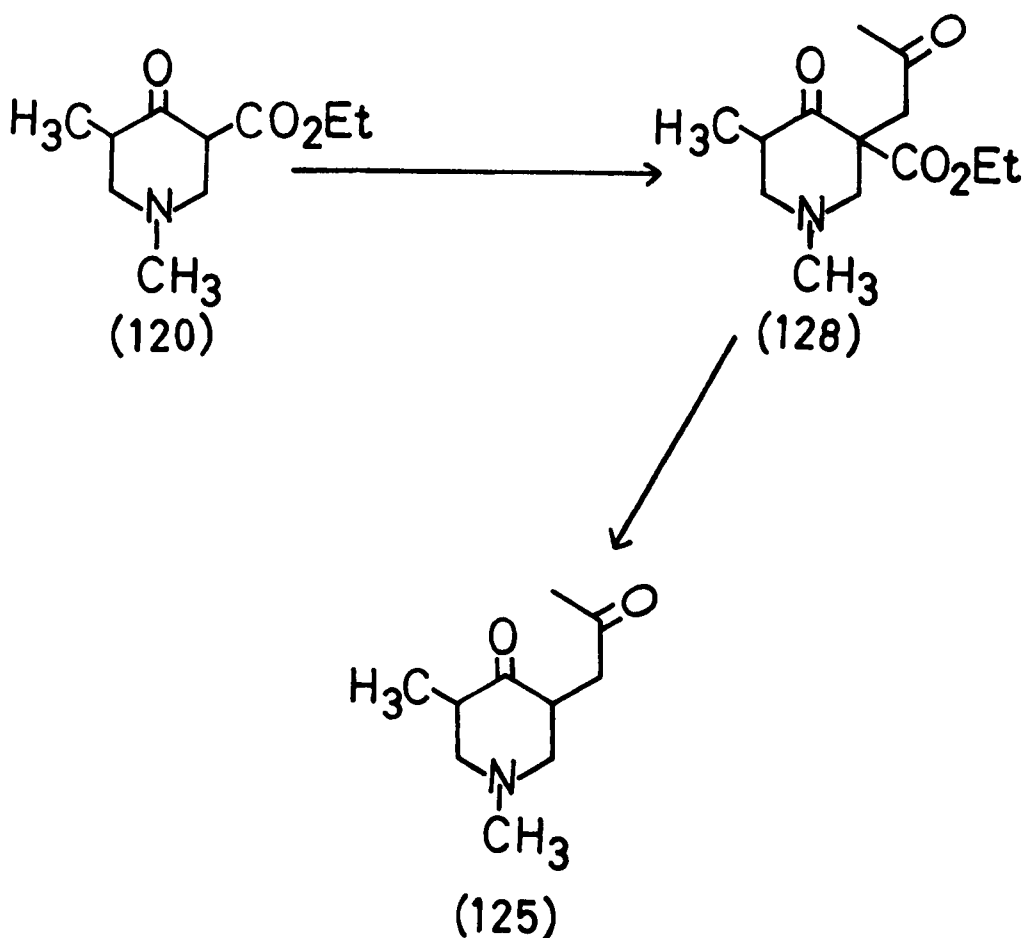
Direct alkylation of the enamine (123) with bromoacetone<sup>84</sup> also gave 3-acetyl-1:5-dimethyl-4-piperidone (125), but when the alkylation with bromoacetone was carried out at room temperature as with propargyl bromide, the yield of 3-acetyl-1:5-dimethyl-4-piperidone (125) was only 21%. In an attempt to increase the yield, different reaction conditions were studied. The effect of room temperature on the reaction and the time of addition of bromoacetone were considered. It was felt that the reactive enamine group would still undergo alkylation at even a lower temperature, while a higher temperature might also promote N-alkylation to an even greater extent. Whereas a very slow addition of bromoacetone would decrease N-alkylation presumably by the complete conversion to the enamine complex (127a) or (127b) so that there would never be an excess of unreacted bromoacetone anytime during the reaction.



Accordingly, the enamine (123) of 1:3-dimethyl-4-piperidone was dissolved in dry benzene under nitrogen. The solution was cooled in an ice-bath and bromoacetone in benzene was added dropwise over a period of 2 to 3 hours. An orange oil began to precipitate from the reaction mixture after 45 minutes. After stirring the mixture for 45 hours, the enamine complex was decomposed by stirring with water for 30 minutes at room temperature. Working up the reaction mixture, a 65% yield of 1:5-dimethyl-3-acetonyl-4-piperidone (125) was obtained. The amount of intractable quaternary material produced by this technique was greatly reduced. The IR spectrum (film) showed C=O absorption at  $1715\text{ cm}^{-1}$ . The NMR spectrum ( $\text{CDCl}_3$ ) showed a  $\text{CH}_3\text{-CO-}$  singlet at 2.2 p.p.m., the  $\text{N-CH}_3$  singlet at 2.4 p.p.m. and  $\text{C-CH}_3$  doublet centred at 1.05 p.p.m.

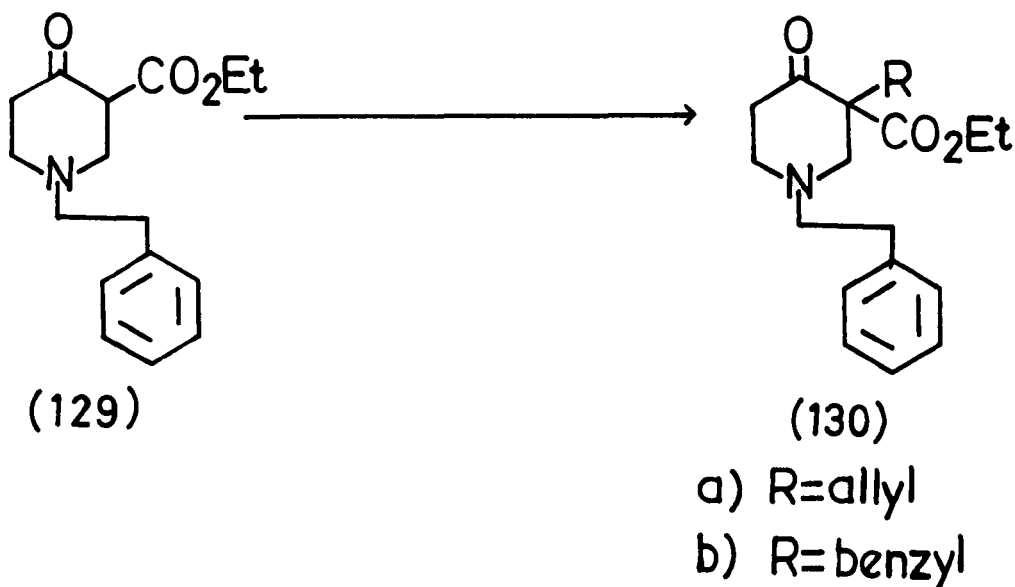
b) BY ALKYLATION OF THE SODIUM SALT OF 1:5-DIMETHYL-3-CARBOETHOXY-4-PIPERIDONE (120).

1:5-Dimethyl-3-acetonyl-4-piperidone (125) was also obtained by the alkylation of the sodium enolate of 1:5-dimethyl-3-carboethoxy-4-piperidone (120) with bromoacetone<sup>84</sup> and subsequent decarboethoxylation of the product, 1:5-dimethyl-3-carboethoxy-3-acetonyl-4-piperidone (128), with dilute hydrochloric acid under nitrogen.



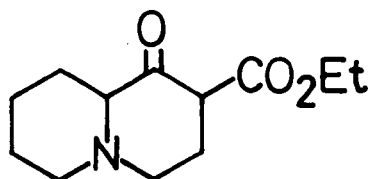


The C-alkylation of basic ketoesters by means of enolate anions is not a satisfactory reaction. McElvain and Barnett<sup>85</sup> found that the reaction of the sodium salt of 1-methyl-3-carboethoxy-4-piperidone with methyl iodide gave N- rather than C-alkylated products. A 48% yield of 1-(2'-phenyl ethyl)3-allyl-3-carboethoxy-4-piperidone (130a) was obtained from the sodium salt of the keto ester (129) and allyl dimethyl anilinium bromide, after boiling in benzene.

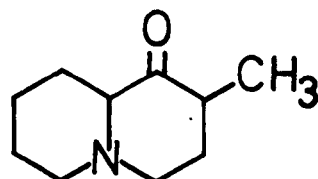


With benzyl dimethyl anilinium chloride, a 72% yield of 1-(2'-phenyl ethyl)3-benzyl-3-carboethoxy-4-piperidone (130b) was obtained.

Clemo and Metcalfe<sup>86</sup> have alkylated the basic ketoester (131) with methyl iodide in the presence of potassium ethoxide and obtained



(131)



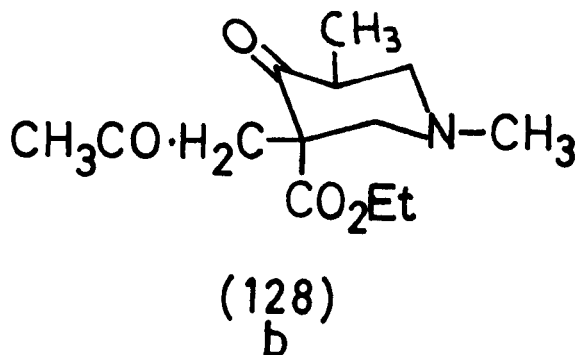
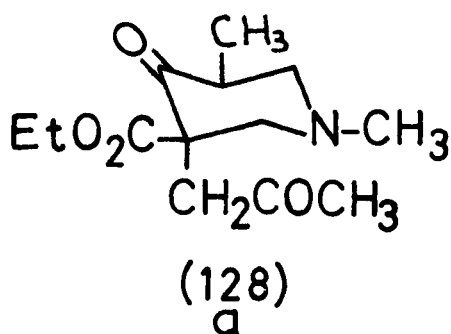
(132)

a 38% yield of the methyl ketone (132).

The alkylation of 1:5-dimethyl-3-carboethoxy-4-piperidone (120) was performed in dry dimethoxy-ethane under nitrogen. Bromoacetone<sup>84</sup> was added dropwise with stirring to a refluxing suspension of the sodium salt of the keto ester (120). After the addition was complete, the mixture was refluxed for 3 hours. Sodium bromide formed was dissolved by the addition of water and the solution extracted with chloroform. Drying and evaporation of the solvent gave a 25% yield of 1:5-dimethyl-3-acetonyl-3-carboethoxy-4-piperidone (128).

In view of this low yield, it was thought that the reaction should be carried out at lower temperature, because heating the reaction mixture could promote N-alkylation to an even greater extent, although it would enhance the rate of the reaction as well. Therefore, bromoacetone<sup>84</sup> was added dropwise over a longer period to a cold-stirred-suspension

of the sodium salt of the keto ester (120). The reaction mixture was stirred at room temperature for 24 hours, it was then heated gently for half an hour. Working up as before, a yield of 69% of 1:5-dimethyl-3-acetyl-3-carboethoxy-4-piperidone (128) was obtained. It was purified by chromatography on Woelm alumina IV. The IR spectrum (film) showed a broad band from  $1710\text{ cm}^{-1}$  to  $1725\text{ cm}^{-1}$  due to the three  $\text{C}=\text{O}$  groups. The NMR spectrum ( $\text{CDCl}_3$ ) showed a  $\text{CH}_3\text{-CO}$  singlet at 2.23 p.p.m., an  $\text{N-CH}_3$  singlet at 2.35 p.p.m., a  $\text{C-CH}_3$  doublet centred at 1.05 p.p.m., a quartet of the ester  $\text{CH}_2$  centred at 4.3 p.p.m., and a triplet of the ester  $\text{CH}_3$  centred at 1.3 p.p.m. The quartet and triplet, due to the ester  $\text{CH}_2$  and ester  $\text{CH}_3$  groups respectively, had a slight shoulder on each of the peaks indicating the presence of epimers (128a) and (128b).

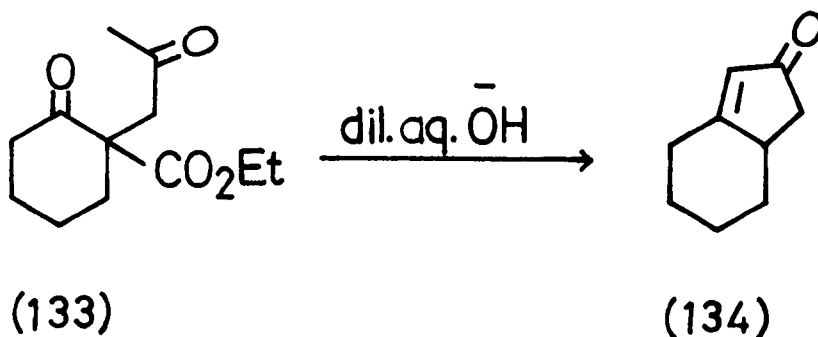


When 1:5-dimethyl-3-acetyl-3-carboethoxy-4-piperidone was heated under reflux with 30% hydrochloric acid in an atmosphere of nitrogen, until the evolution of carbon dioxide ceased, the reaction mixture on basification with dilute ammonia and extraction with chloroform furnished 1:5-dimethyl-3-acetyl-4-piperidone (125) in 50% yield.

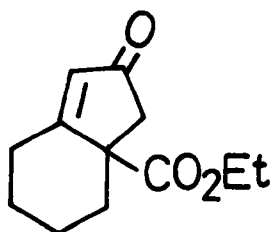
ATTEMPTED CYCLODEHYDRATION OF 1:5-DIMETHYL 3-ACETONYL-

4-PIPERIDONE (125)

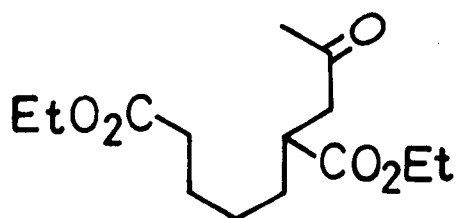
Raphaël and Islam<sup>87</sup> have synthesised 2:4:5:6:7:8-hexahydroindene-2-one (134).



The diketone (133) was cyclised with dilute potassium hydroxide solution with concomitant hydrolysis and decarboxylation of the ester group. This synthesis has recently been repeated by Dauben et al.<sup>88</sup> The attempted cyclisation of the diketone (133) to ethyl 2:4:5:6:7:8-hexahydroindene-2-one-8-carboxylate (135) with sodium ethoxide in ethanol yielded exclusively the product of a reverse Dieckmann reaction, diethyl α-acetonyl-pimelate (136). It was found that this reverse Dieckmann



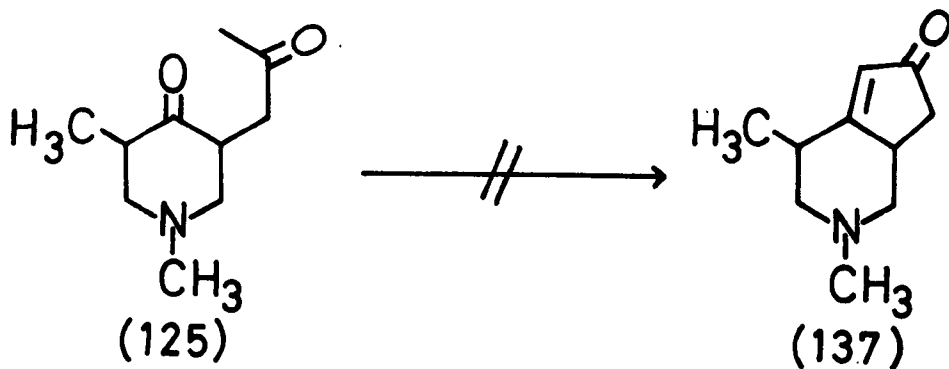
(135)



(136)

reaction could be eliminated if the reaction was conducted in the presence of potassium in tertiary butanol, although some 2:4:5:6:7:8-hexahydroindene-2-one (134) was always produced.

When the cyclisation of 1:5-dimethyl-3-acetyl-4-piperidone (125) was attempted at room temperature using potassium in tertiary butanol, the reaction mixture gave mainly the unchanged starting material.

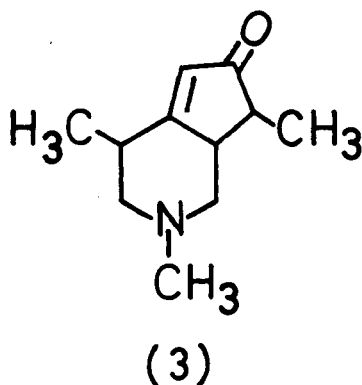


Boiling the solution under reflux for 30 minutes to one hour, produced a darkening of the reaction mixture and a black residue was produced. The crude material was found to be the starting material by its NMR and IR spectra.

With hot dilute sodium hydroxide or potassium hydroxide solution, the reaction mixture yielded some of the starting material and a black intractable tar.

Sodium methoxide in methanol also gave back the unchanged material.

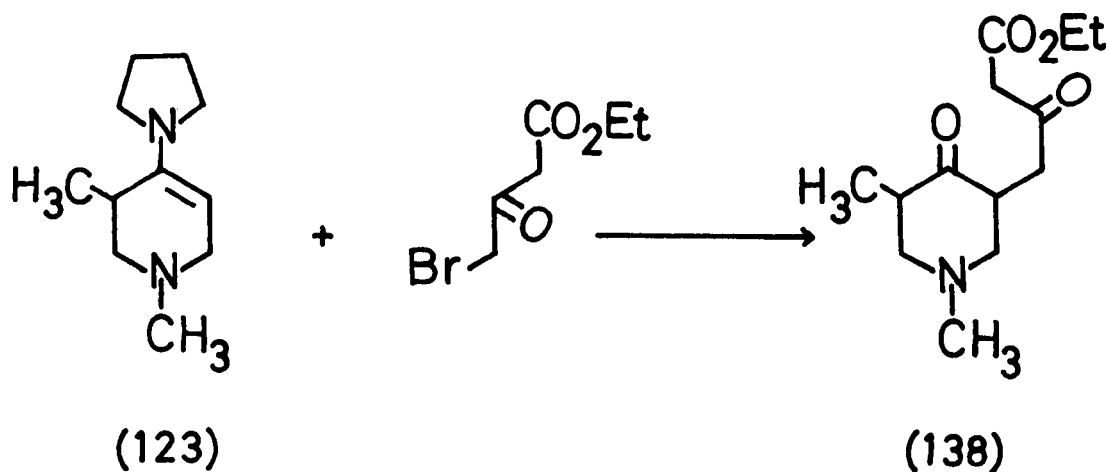
A cyclised compound such as (137)<sup>89</sup> is structurally related to tecomanine (3) and it is known that tecomanine is very unstable to aqueous base.<sup>89</sup>



Attempts at acid-catalysed cyclisation,<sup>90</sup> involving the boiling of 1:5-dimethyl-3-acetonyl-4-piperidone (125) in glacial acetic acid containing varying amounts of hydrochloric acid, were unsuccessful.

Refluxing the diketone (125) in benzene with a small amount of *p*-toluene sulphonic acid using a Dean-Stark apparatus, also failed.

As reported in the preceding discussion, the methyl group of the acetyl side-chain in 1:5-dimethyl-3-acetyl-4-piperidone (125) did not condense with the carbonyl function of the six-membered ring of the same compound. It was, therefore, inferred that the methyl group was not sufficiently active to form the required perhydropyridane system (137) and so an attempt was made to synthesise a compound in which this methyl group would be more active. Such a compound could be obtained by alkylating the enamine (123) of 1:3-dimethyl-4-piperidone with ethyl- $\gamma$ -bromoacetoacetate yielding 1:5-dimethyl-3-(3'-carboethoxyacetyl)-4-piperidone (138).



Such a methylene group between the two carbonyl functions should be more active in condensation reaction. The carboethoxy group could be removed

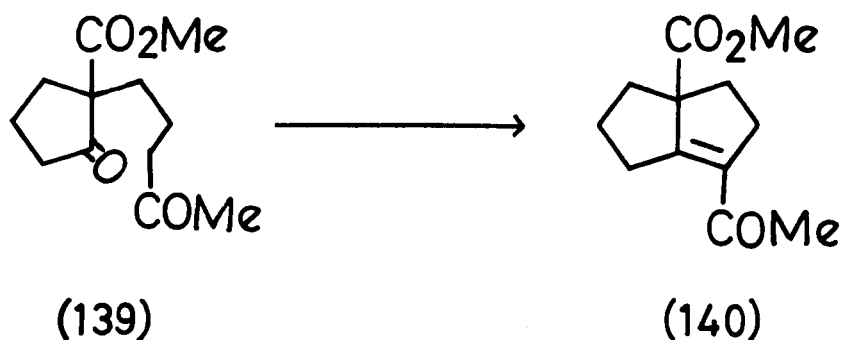


readily by hydrolysis and decarboxylation without bringing about any undesirable change in the structure of the final compound.

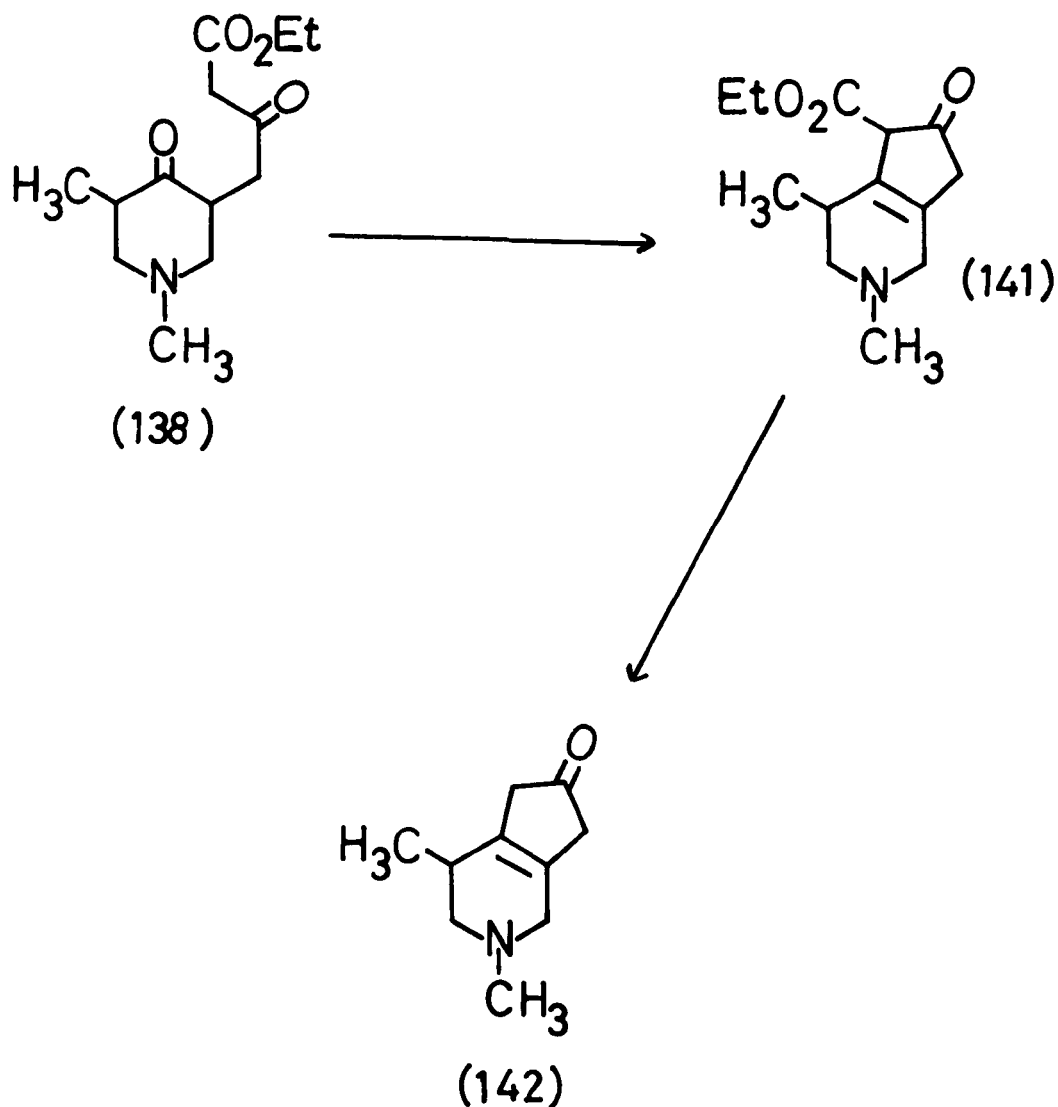
The enamine (123) of 1:3-dimethyl-4-piperidone was alkylated with ethyl- $\gamma$ -bromoacetoacetate which was prepared by the method of Toan and Tefas.<sup>91</sup> The enamine (123) was dissolved in dry benzene under nitrogen and an equivalent quantity of ethyl- $\gamma$ -bromoacetoacetate in dry benzene was added dropwise with stirring and ice-bath cooling. The stirring in this case was continued for 65 hours and then the reaction mixture was worked up as in the case of 1:5-dimethyl-3-acetonyl-4-piperidone (125) yielding about 68% of the desired compound (138) which was purified by passing through Woelm alumina grade IV using benzene as the eluent.

The IR spectrum (film) of the compound (138) showed a broad band from  $1710\text{ cm.}^{-1}$  to  $1730\text{ cm.}^{-1}$  due to the three carbonyl functions. The NMR spectrum ( $\text{CDCl}_3$ ) showed the C- $\text{CH}_3$  doublet centred at 1.02 p.p.m., the N- $\text{CH}_3$  singlet at 2.4 p.p.m., the ethyl ester  $\text{CH}_3$  triplet centred at 1.28 p.p.m., the ethyl ester  $\text{CH}_2$  quartet centred at 4.28 p.p.m. and the  $\text{CH}_2$  singlet between the keto and the ester group of the side-chain at 2.49 p.p.m. The  $\text{CH}_2$  singlet between the keto and the ester groups disappeared when the solution in  $\text{CDCl}_3$  was shaken with a drop of  $\text{D}_2\text{O}$ .

Keir<sup>92</sup> made use of cold concentrated sulphuric acid as the condensing agent for the preparation of (3:3:0)-oct-1(2)-ene-5-carboxylate (140) from 2-(4'-oxopentyl)-2-ethoxycarbonyl-cyclopentanone (139).



Therefore, 1:5-dimethyl-3-(3'-carboethoxy-acetonyl)-4-piperidone (138) was dissolved in ether and then added to concentrated sulphuric acid with stirring and cooled in an acetone-carbon dioxide bath. The stirring was continued for 4 hours. The reaction mixture was poured into ice and washed with chloroform. The acid solution was made alkaline with aqueous ammonia and extracted with chloroform. The chloroform extracts were dried and evaporated under reduced pressure, yielding about 59% of the bicyclic  $\beta$ : $\gamma$  unsaturated ketone (141) which was purified by chromatography on Woelm alumina grade IV.



The IR spectrum (film) showed a broad band from  $1705\text{ cm}^{-1}$  to  $1715\text{ cm}^{-1}$  due to the carbonyl functions, a broad bulge from  $1615\text{ cm}^{-1}$  to  $1625\text{ cm}^{-1}$  due to the unconjugated  $\text{C}=\text{C}$ . The NMR spectrum ( $\text{CDCl}_3$ ) showed no vinyl hydrogen, the  $\text{C}-\text{CH}_3$  doublet was centred at 1.02 p.p.m., the  $\text{N}-\text{CH}_3$  singlet at 2.4 p.p.m., the ethyl ester  $\text{CH}_2$  quartet centred at 4.28 p.p.m. and the ethyl ester  $\text{CH}_3$  triplet centred at 1.28 p.p.m., but the singlet due to the  $\text{CH}_2$  group between the two carbonyls had disappeared.

The bicyclic  $\beta$ : $\gamma$ -ketone (141) was dissolved in 30% hydrochloric acid and heated under reflux in an atmosphere of nitrogen from 2 to 3 hours. The solution was cooled, washed with chloroform, made alkaline with dilute ammonia and extracted with chloroform. The chloroform extracts, on drying and evaporation, furnished 2:4-dimethyl-1:2:3:4:5:7-hexahydro-6H-2-pyridin-2-one (142), purified by chromatography.

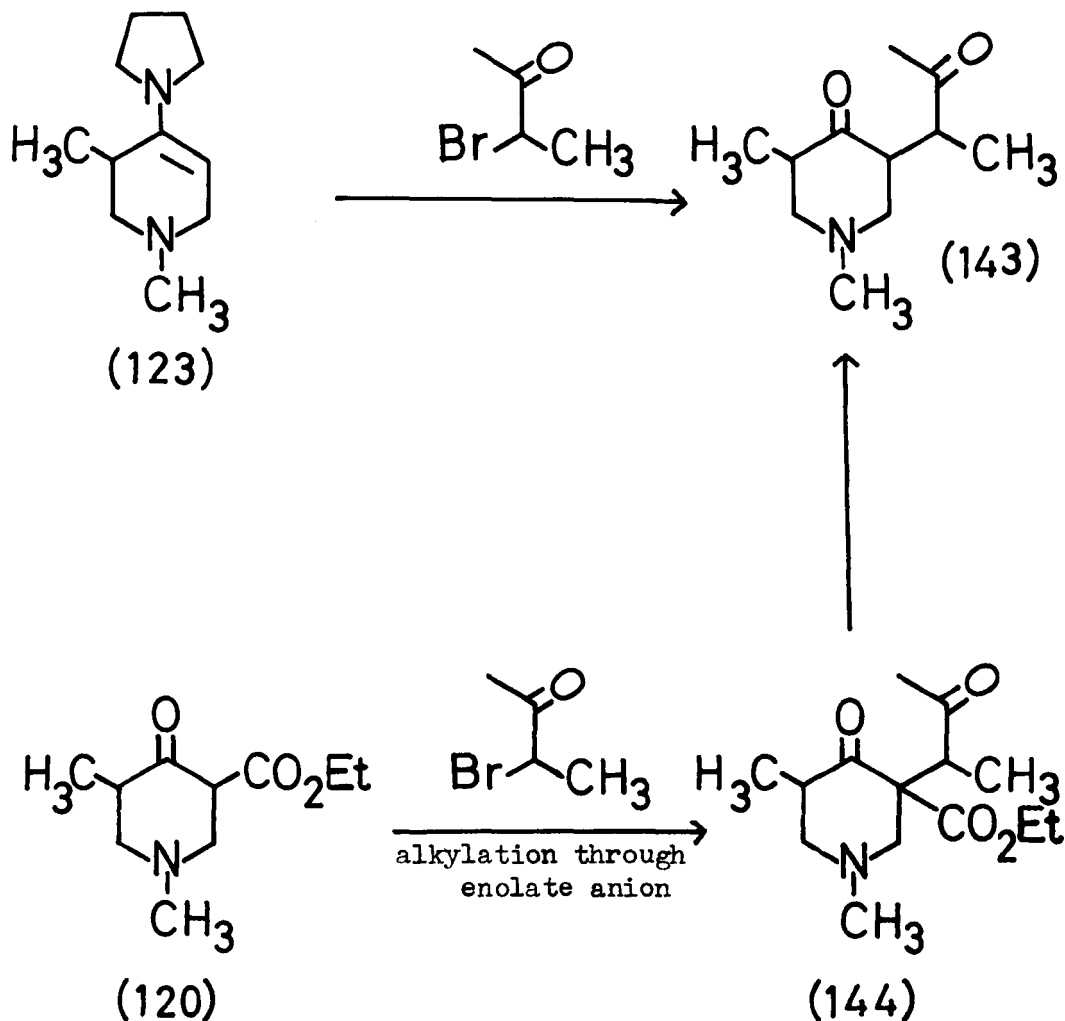
The UV, IR and the NMR spectra were consistent with the structure (142) of the compound.

when the  $\beta$ : $\gamma$ -unsaturated ketone (142) was obtained, it was thought that the presence of the third methyl group (on the acetyl side-chain) might help to cyclise the compound in the required direction yielding an  $\alpha$ : $\beta$ -unsaturated ketone.

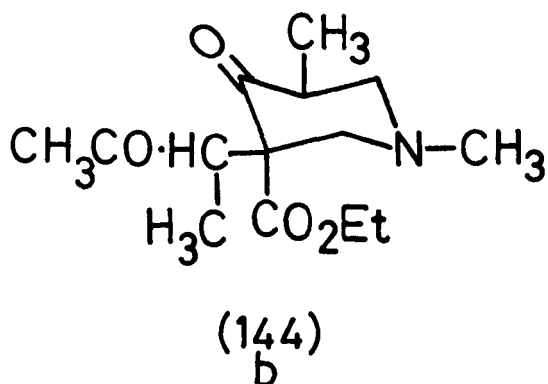
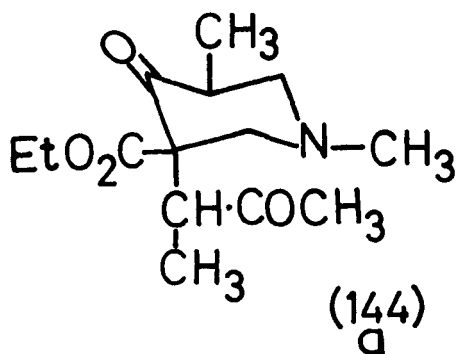
It was decided to synthesise 1:5-dimethyl-3-(1'-methylacetyl)-4-piperidone (143) and this was obtained by alkylation of the pyrrolidine enamine (123) of 1:3-dimethyl-4-piperidone with 3-bromo-2-butanone.<sup>93</sup> The procedure was the same as that used for the alkylation of the enamine (123) with bromoacetone except that, after stirring for 45 hours, the reaction mixture was warmed at 40-50° for a further 4 hours. The reaction mixture yielded 50% of the desired compound (143).

The IR spectrum (film) showed the C=O band at 1712 cm.<sup>-1</sup> due to the two carbonyl functions. The NMR spectrum (CDCl<sub>3</sub>) showed a pair of C-CH<sub>3</sub> doublets centred at 0.96 p.p.m. and 0.98 p.p.m. The N-CH<sub>3</sub> singlet and the CH<sub>3</sub>-CO singlet were superimposed at 2.3 p.p.m. The methyl-acetyl compound (143) could also be obtained by alkylation of the sodium salt of 1:5-dimethyl-3-carboethoxy-4-piperidone (120), with 3-bromo-2-butanone<sup>93</sup> and by subsequent hydrolysis and decarboxylation of the product (144) with hydrochloric acid.

1:5-Dimethyl-3-carboethoxy-3(1'-methyl-acetyl)-4-piperidone was obtained in 50% yield and was purified by chromatography on Woelm alumina grade IV.



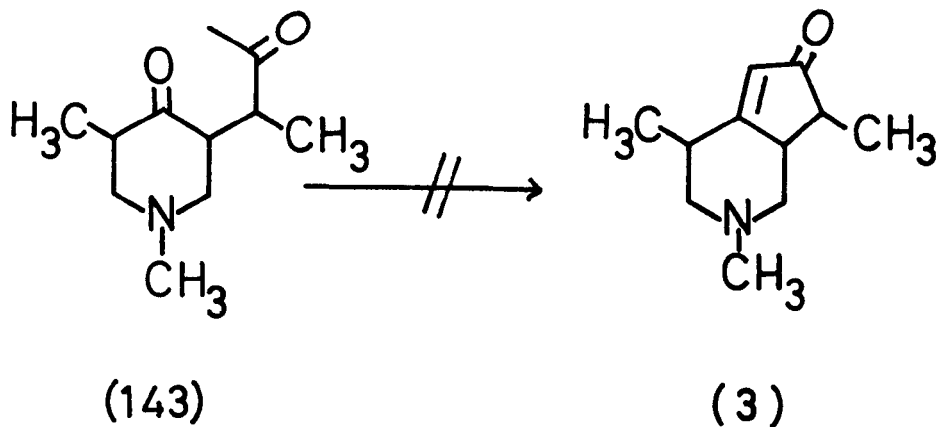
The IR spectrum (film) showed the presence of the C=O band at  $1720\text{ cm}^{-1}$  due to the three carbonyl functions. The NMR spectrum ( $\text{CDCl}_3$ ) showed a  $\text{CH}_3\text{-CO}$  singlet at 2.3 p.p.m., an N- $\text{CH}_3$  singlet at 2.4 p.p.m., the ester  $\text{CH}_2$  quartet centred at 4.35 p.p.m., the ester  $\text{CH}_3$  triplet as well as the two C- $\text{CH}_3$  doublets formed a rather complex splitting pattern from 0.95 p.p.m. to 1.5 p.p.m. Each of the peaks was split further indicating the presence of the epimeric forms (144a) and (144b) as well.



The carboethoxy compound (144) when heated with 30% hydrochloric acid in an atmosphere of nitrogen, yielded 50% of the decarboxylated product (143), 1:5-dimethyl-3-(1'-methyl-acetonyl)-4-piperidone.

The IR and the NMR spectra were consistent with the structure (143) of the compound except that the two C-CH<sub>3</sub> doublets gave a complex splitting pattern in the NMR spectrum. All attempts to equilibrate the compound (143), failed.

Attempted cyclisation of 1:5-dimethyl-3-(1'-methylacetyl)-4-piperidone  
(143) to Tecomanine (3).

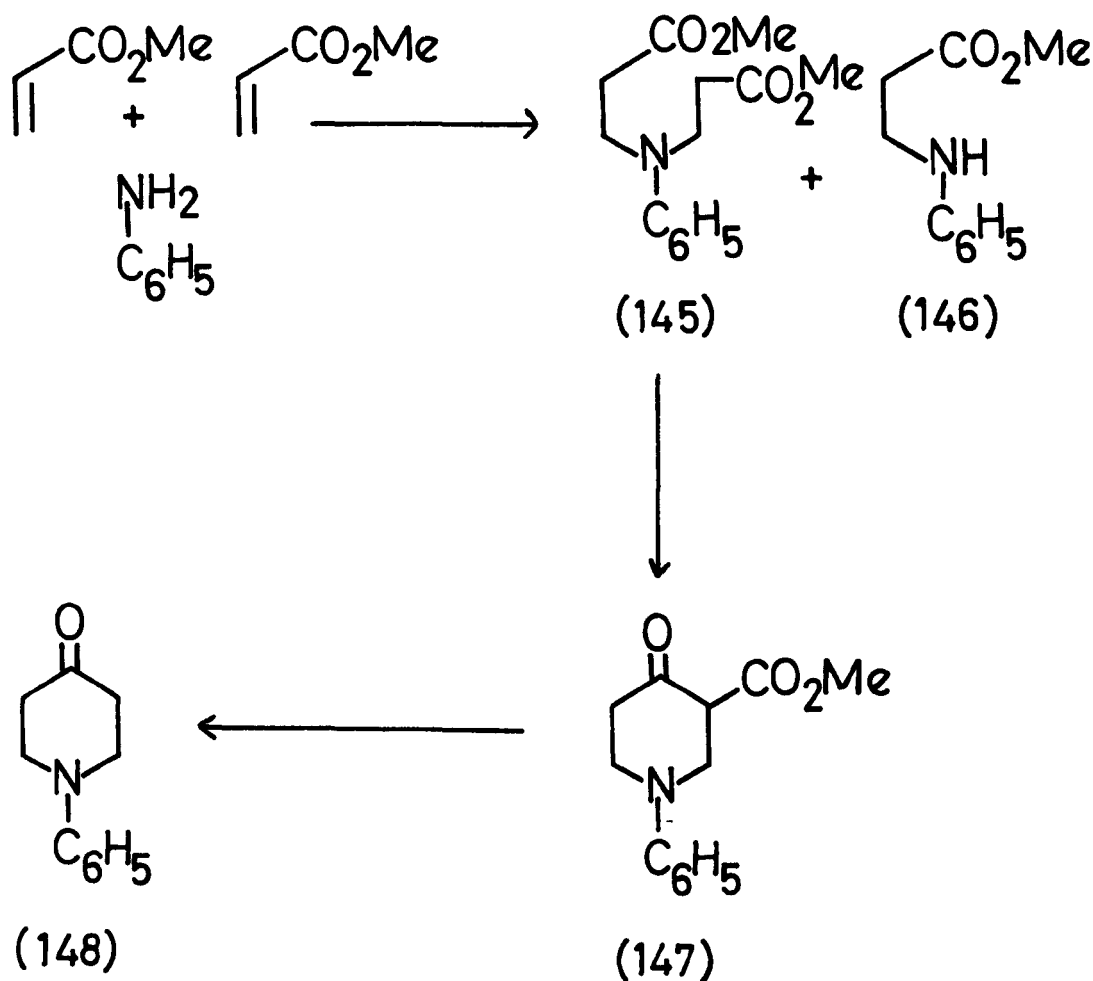


All attempts to cyclise the compound (143) by the same **procedures** as those used for the cyclodehydration of 1:5-dimethyl-3-acetyl-4-piperidone (125), failed.



To study the behaviour of other 3-acetonyl-4-piperidones towards cyclodehydrating reagents, attempts were made to synthesise 3-acetonyl-N-phenyl-4-piperidone (146).

N-Phenyl-4-piperidone (148) was synthesised by the method of Gallagher and Mann<sup>75</sup> starting with methyl acrylate instead of ethyl acrylate.



A mixture of aniline and methyl acrylate was heated under reflux for 28 hours with stirring under nitrogen in glacial acetic acid containing

cuprous chloride. The reaction mixture yielded 60% of di-( $\beta$ -carbomethoxy-ethyl)-phenyl-amine (145) and a small quantity of ( $\beta$ -carbomethoxy-ethyl)-phenyl-amine (146).

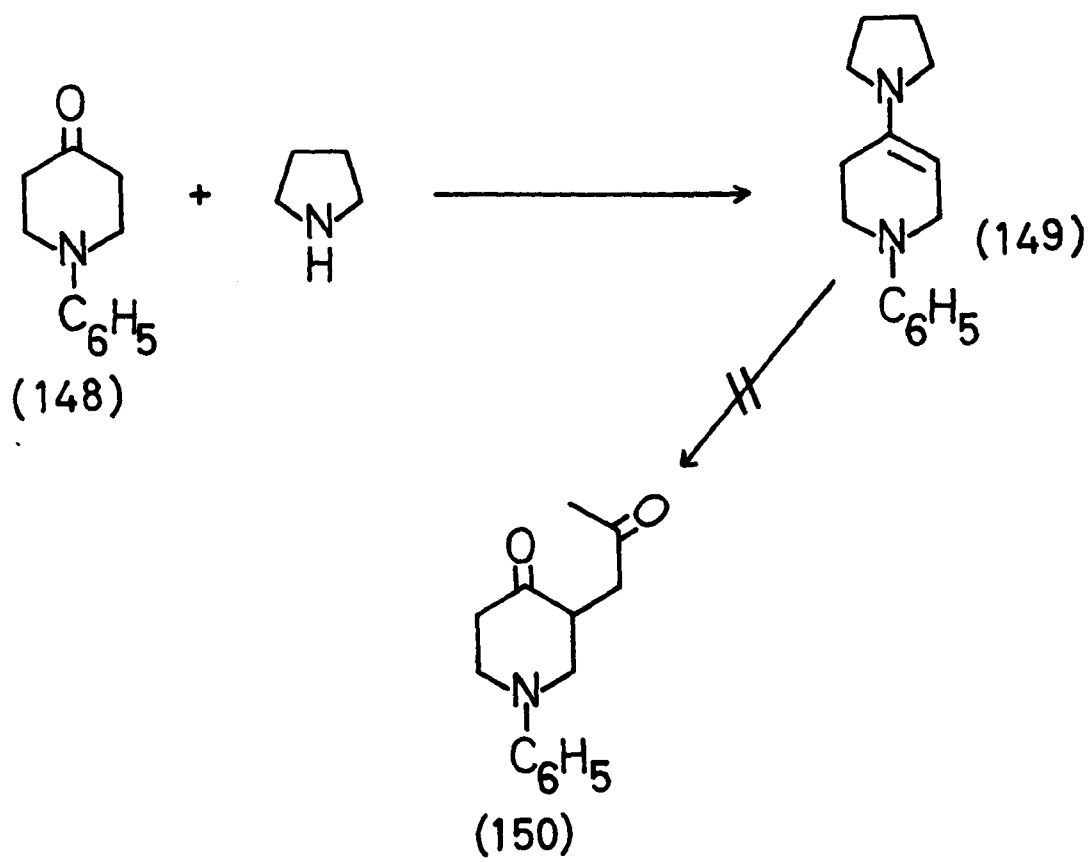
The dimethyl ester (145) was cyclised to 3-carbomethoxy-N-phenyl-4-piperidone (147) in 80% yield by sodium hydride in benzene under the same conditions as those used for the cyclisation of methyl-( $\beta$ -carboethoxy-n-propyl) ( $\beta$ -carboethoxy-ethyl)amine (119).

Hydrolysis and decarboxylation of the keto-ester (147) to N-phenyl-4-piperidone (148) were accomplished in 70% yield by heating with 25% hydrochloric acid.

#### ATTEMPTED SYNTHESIS OF 3-ACETONYL-N-PHENYL-4-PIPERIDONE (150).

N-Phenyl-4-piperidone (148) was converted into the pyrrolidine enamine (149) by heating with pyrrolidine in benzene containing a catalytic amount of *p*-toluene sulphonic acid under nitrogen as before.

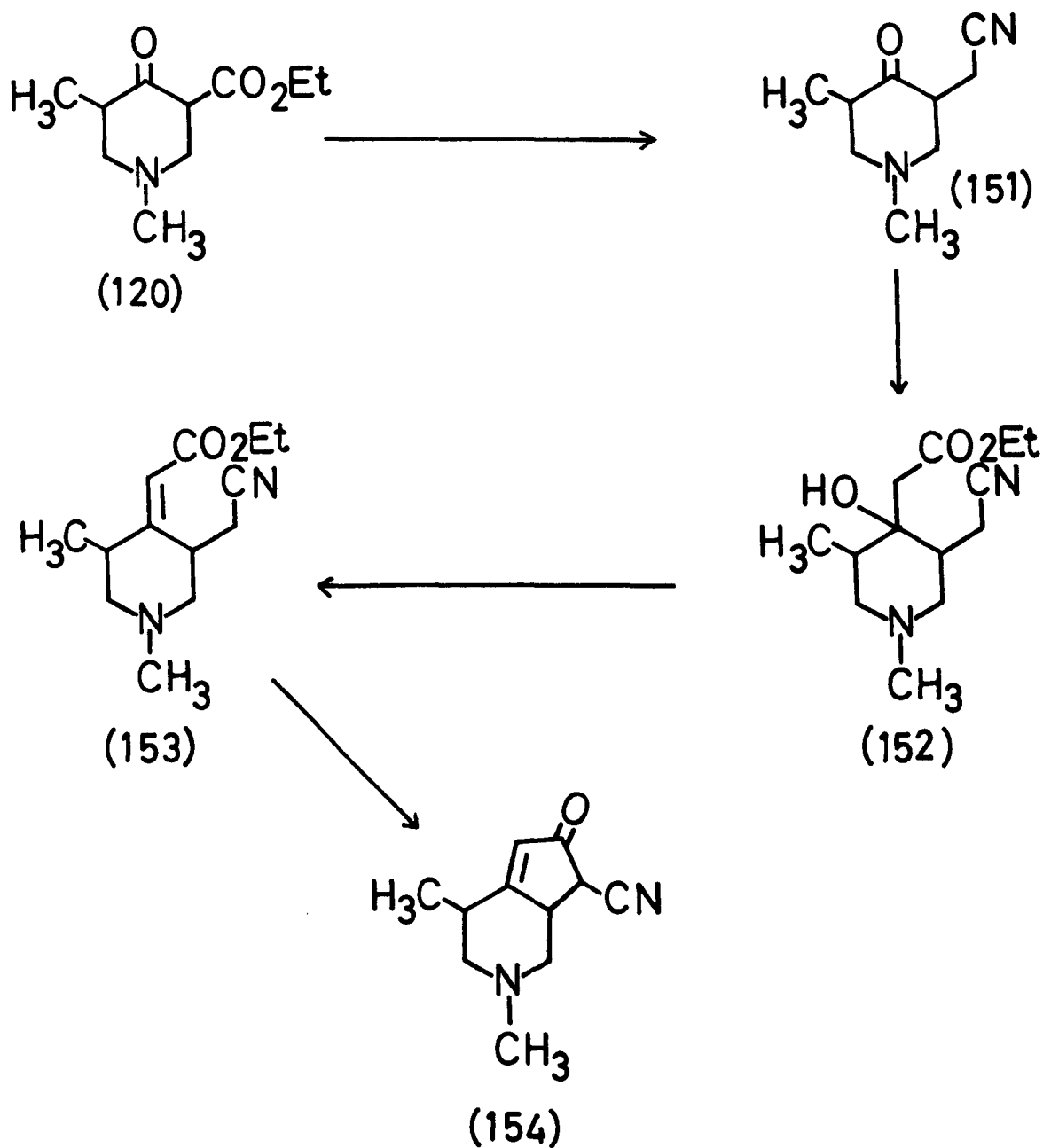
The crude enamine (149) was used for the preparation of 3-acetonyl-N-phenyl-4-piperidone (150). When the alkylation with bromoacetone was performed on the crude enamine (149), the expected product, 3-acetonyl-N-phenyl-4-piperidone (150), could not be obtained. The compound obtained in this alkylation reaction, showed in the IR spectrum a CO band at  $1735\text{ cm}^{-1}$  and a sharp band at  $1625\text{ cm}^{-1}$  and the mono-substituted benzene at  $725\text{ cm}^{-1}$  and  $785\text{ cm}^{-1}$  and the NMR spectrum a 3-proton-singlet ( $\text{CO}-\text{CH}_3$ ) at 2.25 p.p.m., a 2-proton-doublet centred at 4.1 p.p.m. and 9 protons in the aromatic region.



*PART III*

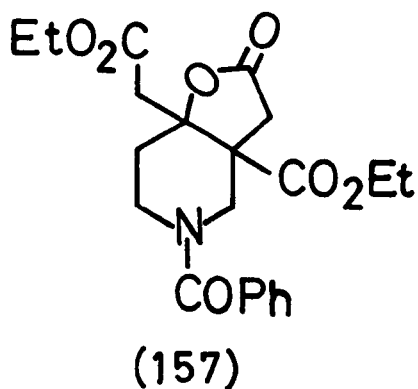
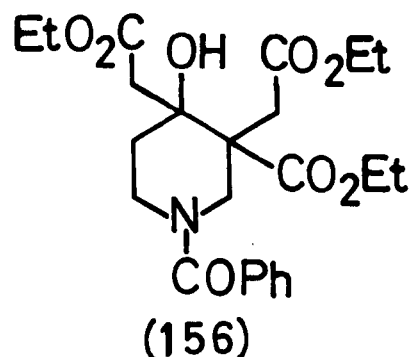
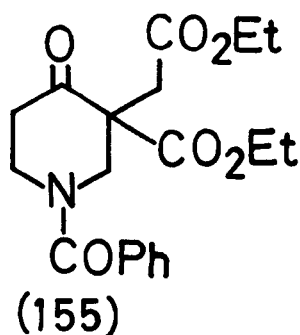
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In another approach to the perhydropyrindane system (154), use was made of the carboethoxy group of the keto ester (120) to prepare 1:5-dimethyl-3-cyanomethyl-4-piperidone (151). It was hoped that this compound (151) would undergo Reformatsky reaction with ethyl bromoacetate to give the corresponding hydroxy ester (152).



The hydroxy ester (152) could then be dehydrated and cyclised to the desired system (154).

When the Reformatsky reaction was performed on the compound<sup>62</sup> (155), instead of the expected product (156) the lactone (157) was obtained by the interaction of the 3-carboethoxy methyl group and the 4-hydroxy group of the compound (156).

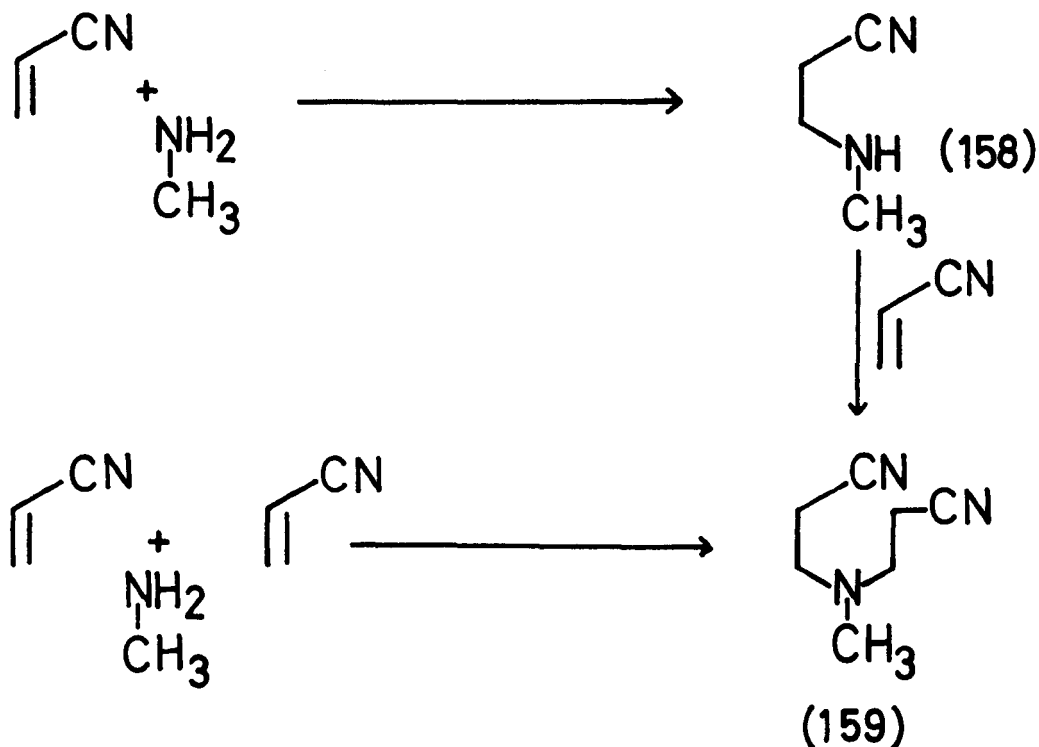


It was thought that the 3-cyanomethyl group would not undergo lactonisation.

Initial experiments of this series were performed on 3-carboethoxy-N-methyl-4-piperidone (161).

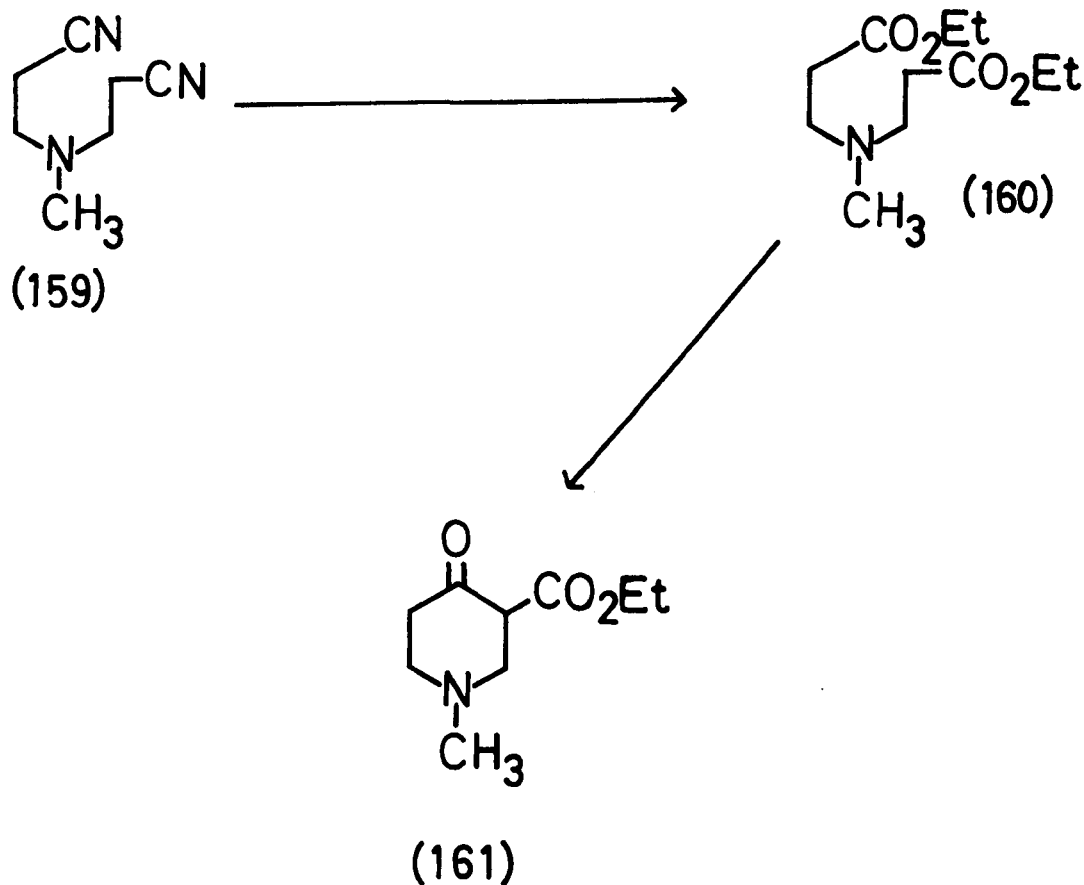
SYNTHESIS OF 3-CARBOETHOXY-N-METHYL-4-PIPERIDONE (161).

( $\beta$ -Cyanoethyl)-methyl-amine (158) was prepared by the method of Cook and Reed.<sup>76</sup> ( $\beta$ -Cyanoethyl)-methyl-amine (158) when heated under reflux with acrylonitrile, gave an 80% yield of di-( $\beta$ -cyano-ethyl)-methyl-amine (159).



Di-( $\beta$ -cyano-ethyl)-methyl-amine (159) was also obtained in good yield when acrylonitrile (2M) was added carefully to the ethanolic solution of methylamine (1M) and allowed to stand for a week.

Di-( $\beta$ -cyano-ethyl)-methyl-amine (159) was converted in 80% yield to the corresponding di-ester (160) by heating with ethanolic hydrogen chloride.



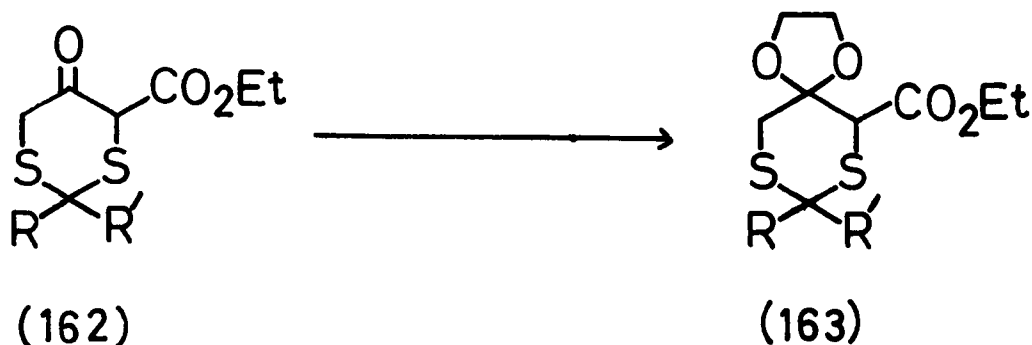
Di-( $\beta$ -carboethoxy-ethyl)-methyl-amine (160) was cyclised to 3-carboethoxy-N-methyl-4-piperidone (161) in 80% yield by using sodium hydride in dry benzene under the same conditions as those described for the cyclisation of methyl-( $\beta$ -carboethoxy-n-propyl)-( $\beta$ -carboethoxy-ethyl)-amine (119).



SYNTHESIS OF THE KETAL (168) OF N-METHYL-3-CARBOETHOXY-METHYL-4-PIPERIDONE

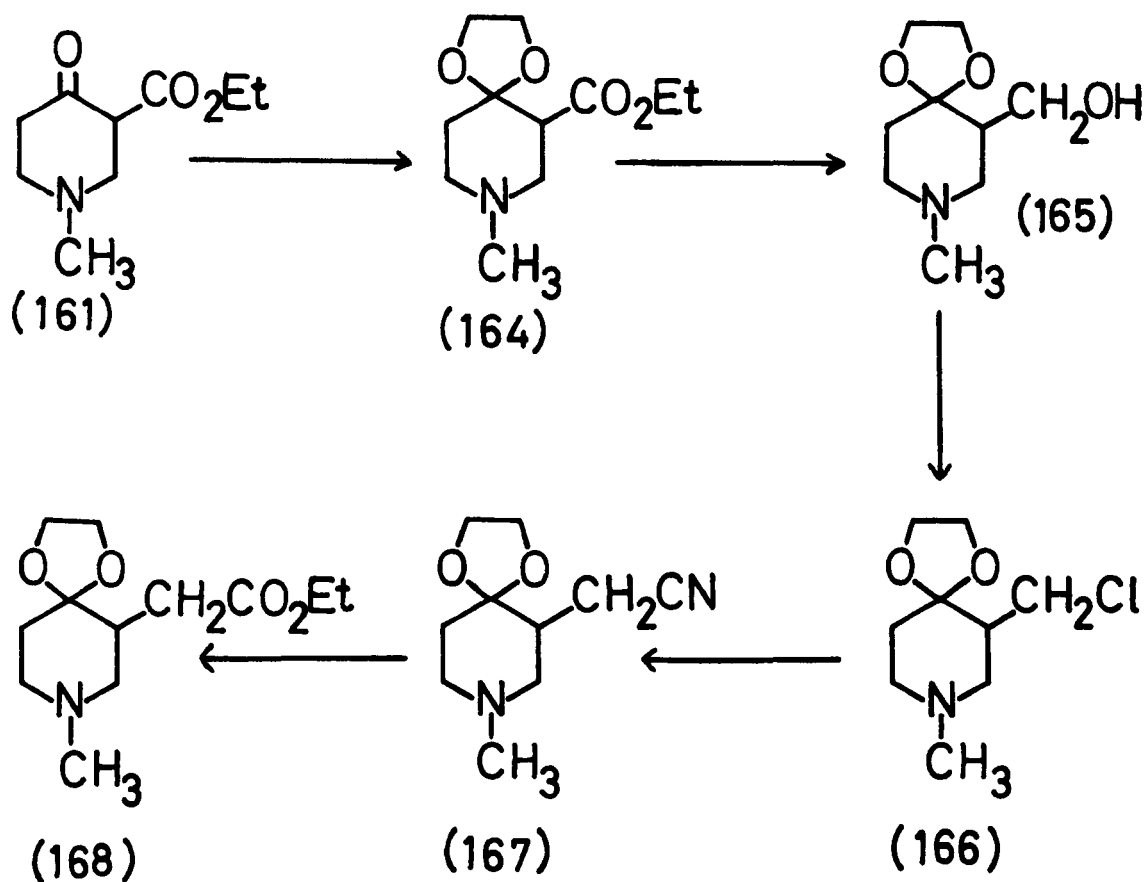
When a benzene solution of the keto-ester (161) containing a small quantity of p-toluene sulphonic acid was heated under reflux for several hours with the equivalent quantity of ethylene glycol, no water separation occurred and on working up the reaction mixture, the unchanged keto-ester (161) was obtained.

Howard and Lindsey<sup>94</sup> converted the keto-ester (162) by reaction with ethylene glycol into the corresponding ketal (163).



Accordingly, N-methyl-3-carboethoxy-4-piperidone (161) was mixed with ethylene glycol, saturated with hydrogen chloride gas, heated at 65-75° for one hour and allowed to stand overnight. The reaction mixture, after working up as usual gave a quantitative yield of the ketal (164).

The IR spectrum (film) showed a rather broad ester C=O band at  $1730\text{ cm}^{-1}$ . The NMR spectrum ( $\text{CDCl}_3$ ) showed the 4-proton ethylene-ketal singlet at 4.00 p.p.m., N-CH<sub>3</sub> singlet at 2.3 p.p.m., ester CH<sub>2</sub> quartet centred at 4.22 p.p.m. and ester CH<sub>3</sub> triplet centred at 1.29 p.p.m.



The ethylene ketal (164) of N-methyl-3-carboethoxy-4-piperidone was converted into the ketal (165) of N-methyl-3-hydroxy-methyl-4-piperidone by reduction with lithium aluminium hydride in refluxing ether. The hydroxy compound (165) was obtained in 85-95% yield.

The IR spectrum showed a broad OH band in the region 3100 to 3400  $\text{cm}^{-1}$  and the absence of the ester C=O band. The NMR spectrum ( $\text{CDCl}_3$ )

showed the ethylene ketal protons as a singlet at 4.05 p.p.m., the N-CH<sub>3</sub> singlet at 2.33 p.p.m. On shaking with a drop of D<sub>2</sub>O, exchange of the OH proton occurred.

The corresponding chloro-compound (166) was obtained from the ketal (165) of N-methyl-3-hydroxymethyl-4-piperidone by reaction with thionyl chloride in chloroform saturated with hydrogen chloride gas. The yield of the chloro-compound was 80%.

The IR spectrum (film) showed a sharp C-Cl band at 720 cm.<sup>-1</sup>. The NMR spectrum (CDCl<sub>3</sub>) showed the ethylene ketal singlet at 4.00 p.p.m. the N-CH<sub>3</sub> singlet at 2.32 p.p.m. and there was no exchange on shaking with D<sub>2</sub>O.

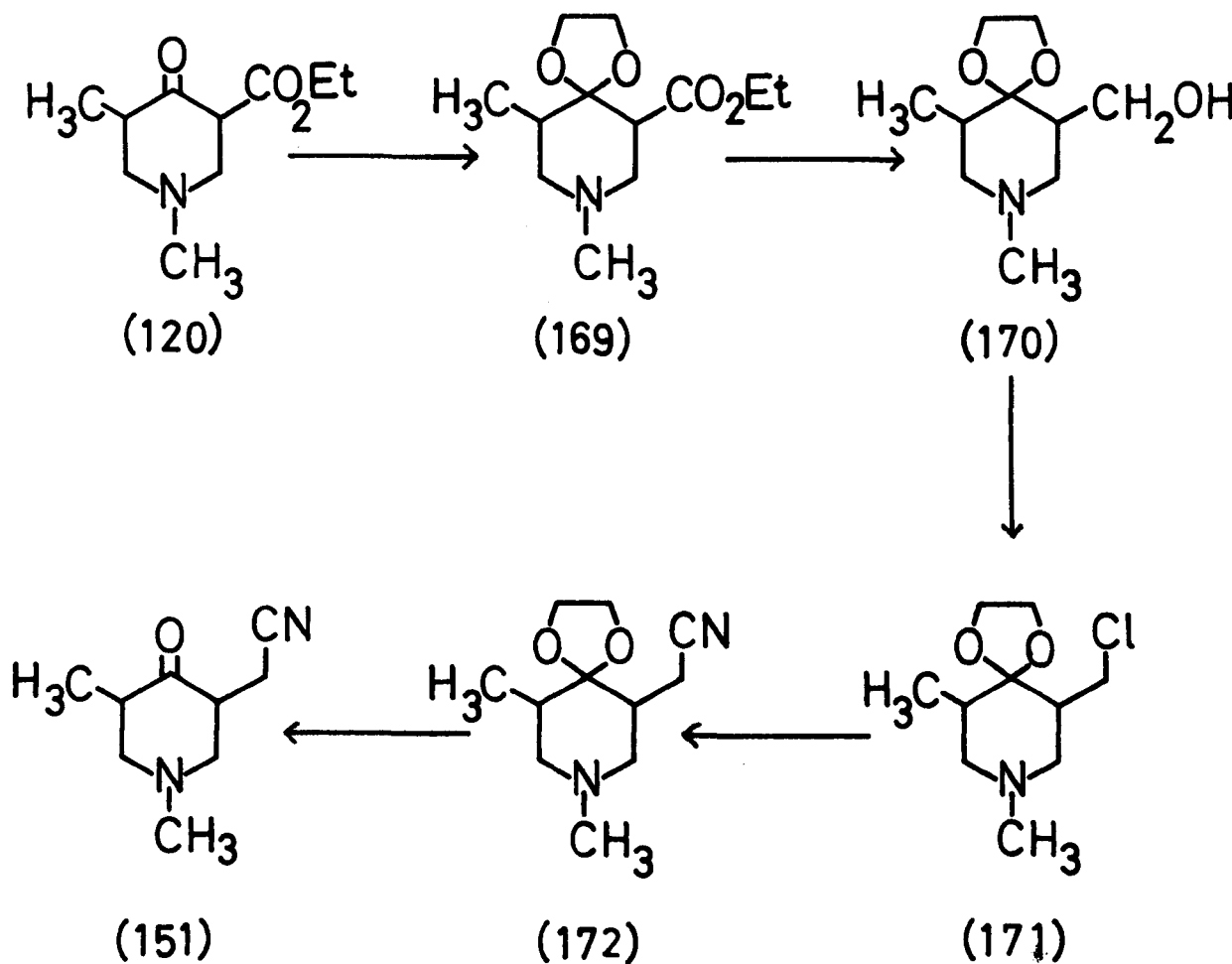
The ethylene ketal (167) of N-methyl-3-cyanomethyl-4-piperidone was prepared from the preceding chloro-compound (166) in 70% yield by reaction with sodium cyanide in dimethyl sulphoxide.<sup>95</sup>

The IR spectrum (film) showed a sharp CN band at 2220 cm.<sup>-1</sup>. The NMR spectrum (CDCl<sub>3</sub>) showed the ethylene ketal as a singlet at 4.02 p.p.m., and the N-CH<sub>3</sub> singlet at 2.32 p.p.m.

The cyano-compound (167) gave the corresponding carboethoxymethyl-compound (168) in 80% yield by heating with ethanolic hydrogen chloride.

The IR and the NMR spectra were consistent with the structure (168) of the ketal of N-methyl-3-carboethoxymethyl-4-piperidone.

SYNTHESIS OF 1:5-DIMETHYL-3-CYANOMETHYL-4-PIPERIDONE (151).



The ethylene ketal (169) of 1:5-dimethyl-3-carboethoxy-4-piperidone was obtained quantitatively in the same way as the ketal (164) of the monomethyl compound.

The IR spectrum (film) showed a rather broad ester C=O band at  $1740\text{ cm}^{-1}$ . The NMR spectrum ( $\text{CDCl}_3$ ) showed the ethylene ketal protons as a singlet at 4.04 p.p.m., N-CH<sub>3</sub> singlet at 2.25 p.p.m., the ester CH<sub>2</sub> quartet centred at 4.26 p.p.m., the ester CH<sub>3</sub> triplet centred at 1.28 p.p.m.

and the C-CH<sub>3</sub> doublet centred at 0.95 p.p.m. The ethylene ketal (170) of 1:5-dimethyl-3-hydroxymethyl-4-piperidone was prepared in 69% yield from the preceding carboethoxy compound (169) by reduction with lithium aluminium hydride in refluxing ether as before.

The IR spectrum (Nujol) showed a broad OH band from 3100 cm.<sup>-1</sup> to 3300 cm.<sup>-1</sup> and the absence of the ester CO band. The NMR spectrum (CDCl<sub>3</sub>) showed the ethylene ketal singlet at 4.02 p.p.m., the CH<sub>2</sub> doublet of the 3-hydroxy-methyl group centred at 3.92 p.p.m., N-CH<sub>3</sub> singlet at 2.25 p.p.m., and the C-CH<sub>3</sub> doublet centred at 0.9 p.p.m. The hydroxyl proton was present as rather broad peak at 4.42 p.p.m. which disappeared on shaking the solution with D<sub>2</sub>O.

The hydroxy compound (170) was converted into the ketal (171) of 1:5-dimethyl-3-chloromethyl-4-piperidone in 80-90% yield by reaction with thionyl chloride in chloroform, saturated with hydrogen chloride, as reported for the N-methyl-3-hydroxy-methyl compound (165).

The IR spectrum (film) showed the sharp C-Cl band at 740 cm.<sup>-1</sup>. The NMR spectrum (CDCl<sub>3</sub>) showed the presence of the ethylene ketal singlet at 4.01 p.p.m., the CH<sub>2</sub> doublet of the 3-chloromethyl group centred at 3.78 p.p.m., the N-CH<sub>3</sub> singlet at 2.28 p.p.m. and the C-CH<sub>3</sub> doublet centred at 0.88 p.p.m. There was no exchange when the solution was shaken with D<sub>2</sub>O indicating the absence of OH proton.

The preceding chloro-compound (171) was added to a sodium cyanide suspension in dry dimethyl sulphoxide at 110° and heated at 135-140° for 3 hours or longer, furnished 78-82% of the ethylene ketal (172) of 1:5-dimethyl-3-cyano-methyl-4-piperidone.

The IR spectrum (film) showed the sharp CN band at  $2265\text{ cm}^{-1}$ .

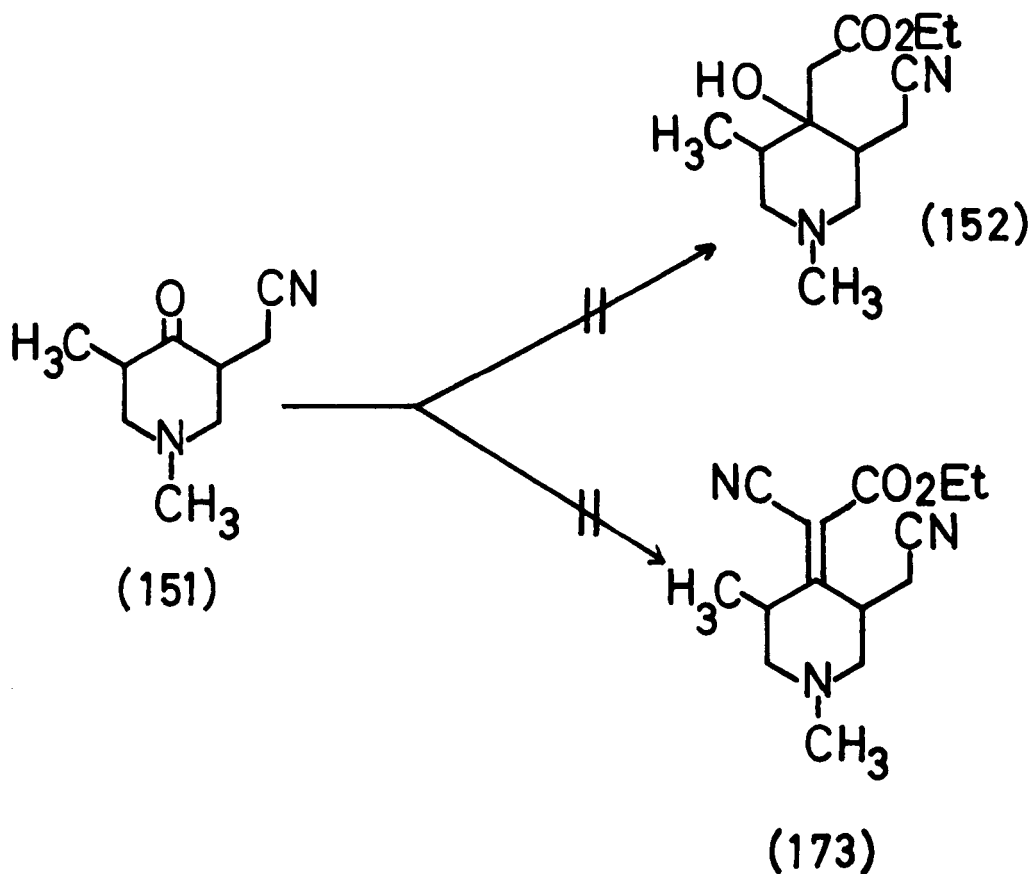
The NMR spectrum ( $\text{CDCl}_3$ ) showed the ethylene ketal singlet at 4.04 p.p.m., the N- $\text{CH}_3$  singlet at 2.29 p.p.m., the C- $\text{CH}_3$  doublet centred at 0.92 p.p.m.

When the ethylene ketal (172) of 1:5-dimethyl-3-cyano-methyl-4-piperidone was heated on the steam bath with 12% hydrochloric acid for 4 hours, a mixture of the starting material (172) and the product (151) was obtained. However, increasing the heating period to 7-9 hours, gave the desired 1:5-dimethyl-3-cyanomethyl-4-piperidone in 60% yield.

The IR and the NMR spectra were consistent with the structure (151) of 1:5-dimethyl-3-cyanomethyl-4-piperidone.

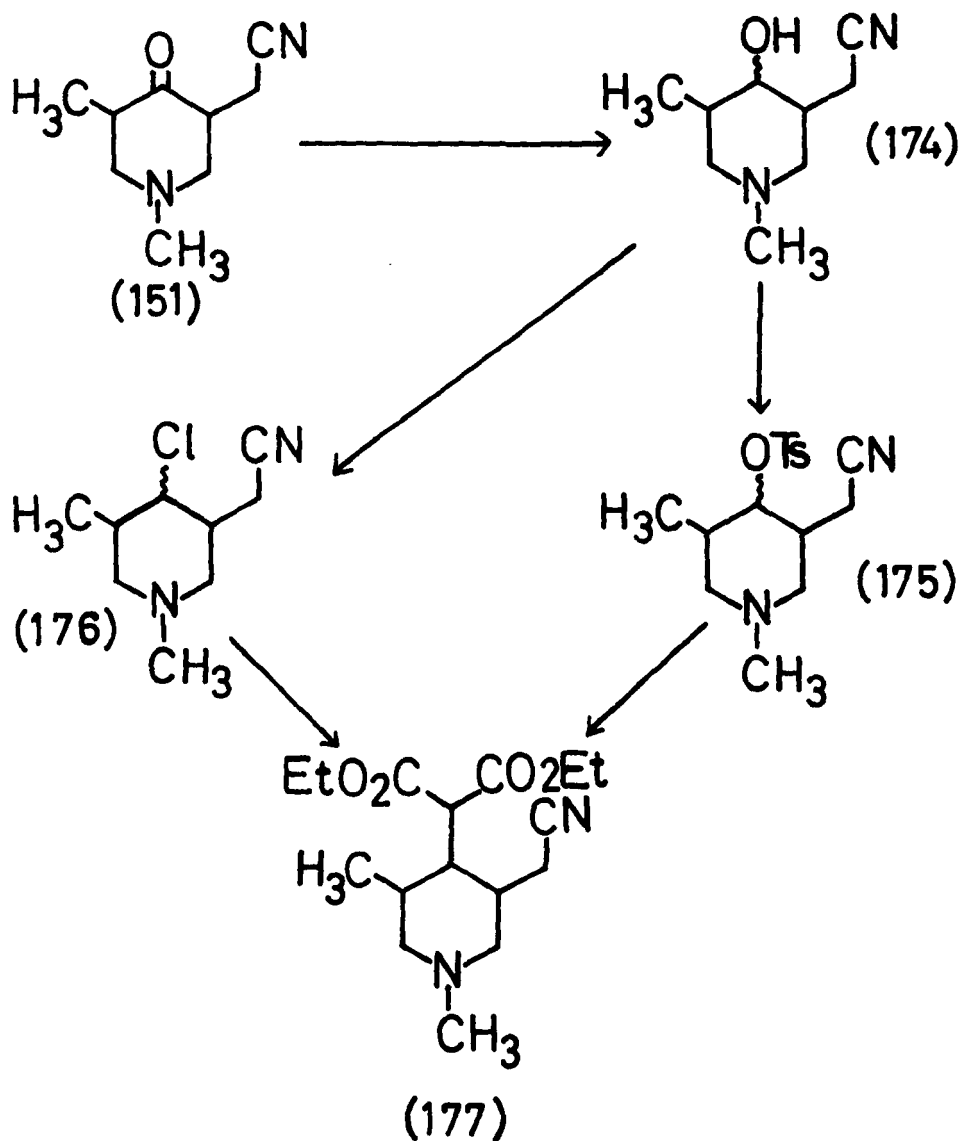
SYNTHESIS OF 1:5-DIMETHYL-3-CYANOMETHYL-4-CHLORO-PIPERIDINE (176).

1:5-Dimethyl-3-cyanomethyl-4-piperidone (151) did not form  
1:5-dimethyl-3-cyanomethyl-4-hydroxy-4-carboethoxy-methyl-piperidine (152)  
62,96  
in a Reformatsky Reaction with ethyl bromoacetate.



Condensation of 1:5-dimethyl-3-cyanomethyl-4-piperidone (151) with ethyl cyano-acetate<sup>97</sup> in refluxing benzene containing a catalytic amount of ammonium acetate or piperidine also did not give the desired product (173).

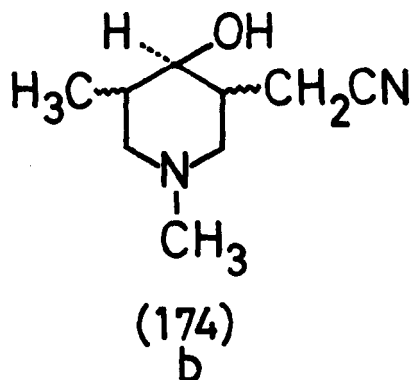
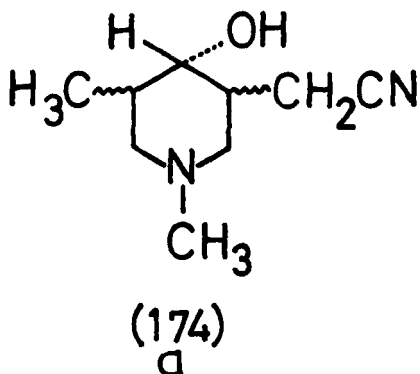
The only alternative route to add a 2-carbon-chain at position-4 was to reduce the ketone (151) to the secondary alcohol (174). The secondary alcohol (174) could then be reacted with the sodium salt of dimethyl malonate through the tosylate (175) or the chloro derivative (176) to give the malonate derivative (177).





Reduction of 1:5-dimethyl-3-cyanomethyl-4-piperidone (151) with sodium boro-hydride in methanol at  $0^{\circ}$  afforded 80-85% of 1:5-dimethyl-3-cyanomethyl-4-hydroxy-piperidine (174).

The IR spectrum (film) showed a broad OH band from 3100-3500  $\text{cm}^{-1}$ , the CN band at 2260  $\text{cm}^{-1}$  and no CO band. The NMR spectrum ( $\text{CDCl}_3$ ) showed an N- $\text{CH}_3$  singlet at 2.33 p.p.m., C- $\text{CH}_3$  doublet appeared as a complex splitting pattern possibly due to the presence of isomeric forms (174a and 174b).



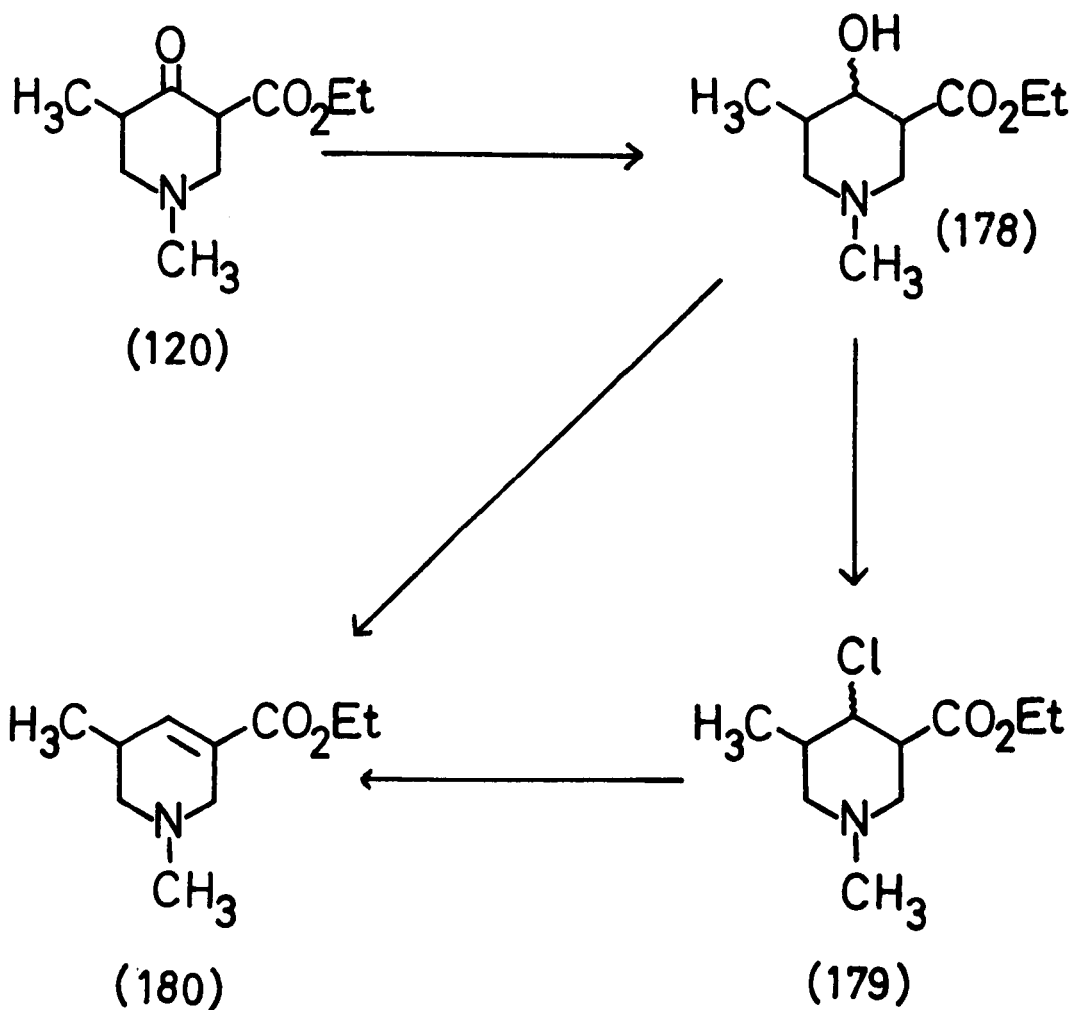
On shaking with  $\text{D}_2\text{O}$  an exchange of the hydroxyl proton occurred.

The secondary alcohol (174) did not form the tosylate (175) on treatment with p-toluene-sulphonyl chloride in anhydrous pyridine for 24-72 hours at room temperature. The chloro-derivative (176) could not be obtained either, when the reaction with thionyl chloride was

carried out in chloroform or benzene under the same conditions as those described for the conversion of the ketal (165) of N-methyl-3-hydroxy-methyl-4-piperidone into the corresponding chloro compound (165). It was, therefore, decided to use 1:5-dimethyl-3-carboethoxy-4-hydroxy-piperidine (178) as a model compound to find the optimum conditions for the reaction of thionyl chloride with 1:5-dimethyl-3-cyanomethyl-4-hydroxy-piperidine (177).

1:5-Dimethyl-3-carboethoxy-4-hydroxy-piperidine (178) was obtained in 80-85% yield by reduction of 1:5-dimethyl-3-carboethoxy-4-piperidone (120) with sodium borohydride in methanol at 0°.

The IR spectrum showed a broad OH band from 3150-3500  $\text{cm}^{-1}$ , and a broad ester CO band at 1725  $\text{cm}^{-1}$ . The NMR spectrum ( $\text{CDCl}_3$ ) showed a  $\text{N-CH}_3$  singlet at 2.25 p.p.m., the  $\text{C-CH}_3$  doublet centred at 1.05 p.p.m., the ester  $\text{CH}_2$  quartet centred at 4.29 p.p.m., and the ester  $\text{CH}_3$  triplet centred at 1.3 p.p.m. The hydroxyl proton appeared as a broad peak at 3.5 p.p.m. which disappeared on shaking with  $\text{D}_2\text{O}$ .



4-Hydroxy-piperidine (178) was then treated with thionyl chloride in chloroform or in benzene, under the same conditions as those described for the conversion of the primary hydroxy compound (165) to the corresponding chloro-compound (166). The reaction mixture yielded 1:5-dimethyl-3-carboethoxy-tetrahydro-pyridine (180) in both cases. A consistent analysis on the compound (180) could not be obtained and the structure (180) is based solely on IR and NMR data.

The IR spectrum (film) showed a broad ester CO band at  $1710\text{ cm.}^{-1}$  and a very sharp band at  $1658\text{ cm.}^{-1}$  due to C=C presumably due to the  $\alpha:\beta$ -unsaturated ester. The NMR spectrum ( $\text{CDCl}_3$ ) showed an N-CH<sub>3</sub> singlet at 2.4 p.p.m., a C-CH<sub>3</sub> doublet centred at 1.08 p.p.m., the ester CH<sub>2</sub> quartet centred at 4.28 p.p.m., the ester CH<sub>3</sub> triplet centred at 1.3 p.p.m. and the vinyl hydrogen appeared as a rather broad peak at 6.96 p.p.m.

However, brief treatment (15-30 minutes) of the secondary alcohol (178) with thionyl chloride in chloroform, without saturating the solvent with hydrogen chloride gas, afforded 70% of 1:5-dimethyl-3-carboethoxy-4-chloro-piperidine (179) on working up the reaction mixture at room temperature.

The IR spectrum (film) showed the C-Cl band at  $730\text{ cm.}^{-1}$  and the ester CO band at  $1725\text{ cm.}^{-1}$ . The NMR spectrum ( $\text{CDCl}_3$ ) showed the C-CH<sub>3</sub> doublet centred at 1.02 p.p.m., an N-CH<sub>3</sub> singlet at 2.33 p.p.m., the ester CH<sub>2</sub> quartet centred at 4.28 p.p.m. and the ester CH<sub>3</sub> triplet centred at 1.31 p.p.m.

The chloro-compound (179) also gave the  $\alpha:\beta$ -unsaturated ester (180) on distillation.

When 1:5-dimethyl-3-cyanomethyl-4-hydroxy-piperidine (174) was treated with thionyl chloride in chloroform at room temperature, the unchanged starting material was obtained. However, refluxing the hydroxy-compound (174) with thionyl chloride in chloroform, gave 60-70% of 1:5-dimethyl-3-cyanomethyl-4-chloro-piperidine (176).

The IR spectrum (film) showed a sharp C-Cl band at  $730\text{ cm.}^{-1}$  and a sharp CN band at  $2250\text{ cm.}^{-1}$ . The NMR ( $\text{CDCl}_3$ ) showed an N-CH<sub>3</sub> singlet

at 2.33 p.p.m., the expected  $\text{O-CH}_3$  doublet gave a sub-splitting pattern centred at 1.08 p.p.m.

1:5-Dimethyl-3-cyanomethyl-4-chloropiperidine (176) when treated with the sodium salt of diethyl malonate in refluxing absolute ethanol for 14 hours, did not give the malonate derivative (177). Refluxing 1:5-dimethyl-3-cyanomethyl-4-chloropiperidine (176) with the sodium salt of diethyl malonate in dry dimethoxyethane for 4 days also failed to give the desired compound (177).

## EXPERIMENTAL

### PRELIMINARY NOTES

Melting points were determined on a Kofler block. Both the melting points (m.p. ) and the boiling points (b.p. ) are uncorrected.

Infrared absorption (IR) spectra were measured with Perkin Elmer Infracord, 221 and 257 spectrometers. The spectra of solids were determined as Nujol mulls (Nujol) or in solution (e.g.  $\text{CCl}_4$ ). The spectra of liquids were determined as liquid films (film) or in solution (e.g.  $\text{CCl}_4$ ).

Ultraviolet absorption (UV) spectra were measured as a Unicam SP 700 instrument.

Nuclear magnetic resonance (NMR) spectra were recorded on a Perkin Elmer 60 megacycle instrument and are quoted in parts per million (p.p.m.) from an internal tetramethyl silane standard (= 0 p.p.m.).

Analytical gas-liquid partition chromatography (VPC) was performed on a 10 ft. spiral glass column packed with Gaschrome P coated with 1% SE-30 silicone grease.

All reactions involving dry solvents were carried out in an atmosphere of nitrogen.

Sodium hydride was used as a 50% dispersion by weight in liquid paraffin.

Microanalyses were carried out by Drs. Weiler and Strauss of Oxford and by Mr. J. Boulton of Keele University.



Trans- $\Delta^{4:5}$ -Tetrahydrohomophthalic Anhydride (96).

Two different methods were used for the preparation of this compound. Hermanek and Trojanek<sup>49</sup> employed dimethyl glutaconate<sup>50</sup> and butadiene as the starting material, whereas Belleau and Puranen<sup>51</sup> started with cis- $\Delta^4$ -tetrahydrophthalic anhydride.<sup>52</sup>

Trans- $\Delta^{4:5}$ -Tetrahydrohomophthalimide (97).

a) In one method, the preceding anhydride was converted into the corresponding imide m.p.  $231-3^\circ$  (dec.) (lit. m.p.  $236-8^\circ$  dec.) by aqueous ammonia.<sup>49</sup>

b) In another method, the anhydride (96) (3 g.) was mixed with urea (3 g.) in a boiling tube fitted with a long air condenser, the top-end of which carrying a small funnel containing glass-wool. The tube was warmed slowly in an oil bath until the whole mass melted. The molten mass was then heated strongly at about  $190^\circ$ , when the imide began to sublime and condensed on the side of the air condenser. The sublimed mass was collected and recrystallised from benzene. The yield of the imide, m.p.  $231-3^\circ$ , was 2 g.

Attempted Epoxidation of Trans- $\Delta^{4:5}$ -Tetrahydrohomophthalimide (98).

a) Tetrahydrohomophthalimide (0.5 g.), being insoluble in ether, was dissolved in dry benzene (5 ml.). To this solution was added ethereal monoperphthalic acid (8 ml.) dropwise and the whole made up to 25 ml. with ether and left at  $0^\circ$ . After some time a

grey solid began to appear at the bottom. This was filtered off and the NMR showed it to be the starting material.

b) Using the same quantities of the reactants as in (a), the whole procedure was repeated using benzene except for the ethereal monoperphthalic acid. The reaction mixture kept at 0° for 5 days. The solution was washed with 2N sodium hydroxide solution and then with water and dried. Evaporation of the solvents under reduced pressure gave the starting material.

c) The reaction was also performed in an immiscible mixture of methanol and ether. Working up the reaction mixture furnished the starting material.

#### 4-Methoxy-Cinnamic Acid (102).

Prepared by the procedure of Robinson and Schinoda.<sup>57</sup>

#### $\beta$ (p-Methoxy-Phenyl)Propionic Acid (103).

Adams' catalyst (0.120 g.) was added to a suspension of 4-methoxy-cinnamic acid (11.4 g.) in methanol (100 ml.) and hydrogenated at atmospheric pressure and room temperature. After the required amount of hydrogen was taken up and further absorption

stopped, the catalyst was filtered off and the solution concentrated to about 20 ml. under reduced pressure. The concentrate was then diluted to about 4 times with water. The crystalline mass was filtered off and recrystallised from hot water and dried. The yield of  $\beta$ -(p-methoxy-phenyl)propionic acid m.p.  $108-9^{\circ}$  was 8 g.

$C_{10}H_{12}O_3$  requires: C, 66.67; H, 6.67%

found: C, 66.47; H, 6.56%

Attempted preparation of  $\beta$ -(4-Methoxy-Phenyl)Ethyl-Amine (104).

To a solution of  $\beta$ -(p-methoxy-phenyl)propionic acid (20 g.) in concentrated sulphuric acid (166 ml.) was added chloroform (332 ml.) with stirring. The temperature was raised to  $45^{\circ}$  and 10.8 g. of sodium azide was added in small portions with vigorous stirring over a period of 2 hrs. During the addition, the temperature was maintained between  $40-45^{\circ}$ . After the addition was complete, the stirring was continued for another 1.5 hours at the same temperature.

The mixture was cooled in ice to  $0^{\circ}$  and ice (700 g.) was added with vigorous stirring. The organic layer was separated and the aqueous layer was washed twice with chloroform. The chloroform extracts were dried and evaporated under reduced pressure giving 15 g. of the starting material.

The acid solution was cooled and made strongly alkaline by the addition of 75% NaOH, maintaining the temperature between  $5-20^{\circ}$ . The alkaline solution was extracted with chloroform. The organic extracts were dried and evaporated leaving a black intractable tar (2 g.).

$\beta$ -(p-Methoxy-Phenyl)Nitro-Styrene (105).

Prepared according to the methods of Rosenmund<sup>60a</sup> and Knoevenagel and Walter.<sup>60b</sup>

$\beta$ -(p-Methoxy-Phenyl)Nitro-Ethane (106).

The preceding nitrostyrene (5 g.) was hydrogenated over Adams' catalyst in ethanol at room temperature. The amount of hydrogen required for the double bond was taken up quite readily and no more hydrogen was absorbed even after several hours. The Adams' catalyst was filtered off, and ethanol removed under reduced pressure. The residue was recrystallised from ethanol, m.p.  $121^{\circ}$ .

$C_9H_{11}O_3N$  requires: C, 59.67; H, 6.08; N, 7.73%

found: C, 59.52; H, 6.0; N, 7.81%

$\beta$ -(p-Methoxy-Phenyl)Ethyl-Amine (104).

A solution of  $\beta$ -(p-methoxy-phenyl)nitroethane (3 g.) in anhydrous ether (Soxhlet extraction technique) was added at a rapid reflux rate to a well stirred suspension of lithium aluminium hydride (2 g.) in 200 ml. of anhydrous ether. About 18 hrs. were required for complete addition. Excess lithium aluminium hydride was decomposed by the cautious addition

of excess ethyl acetate. The inorganic complex was dissolved carefully in 10% sulphuric acid (200 ml.). The ether layer was separated. The acid solution was made strongly alkaline and extracted with ether. The ether extracts were dried and evaporated to yield the amine (2 g.), b.p.  $133-5^{\circ}/13$  mm (lit.<sup>61a</sup> b.p.  $126/8^{\circ}/10$  mm.).

Methyl( $\beta$ -Carboethoxy-n-Propyl)Amine (117).

a) Methylamine (33% ethanolic, 46 g.) was added to ethyl methacrylate (57 g.) and absolute ethanol (90 ml.). The resulting solution was kept at room temperature. On the ninth day, excess of ethanol was removed under reduced pressure and the residue distilled to yield methyl( $\beta$ -carboethoxy-n-propyl)amine (60 g., 85%) b.p. 70-72°/13 mm; and di( $\beta$ -carboethoxy-n-propyl)methylamine (118) (4.66 g.) b.p. 140-142° at the same pressure.

In several runs, the yield of methyl( $\beta$ -carboethoxy-n-propyl)amine varied from 80-86%.

b) When this reaction mixture was worked up after four days,<sup>71a</sup> a lower yield of the monoester was obtained.

Methyl( $\beta$ -carboethoxy-n-propyl)amine,  $C_7H_{15}O_2N$ , requires

C, 57.9; H, 10.3; N, 9.65%

found: C, 57.7; H, 9.97; N, 9.60%

$C_7H_{15}O_2N.HCl$  requires: C, 46.28; H, 8.81, N, 7.7%

found: C, 46.0; H, 8.88; N, 7.7%

Di( $\beta$ -carboethoxy-n-propyl)methylamine,  $C_{13}H_{25}O_4N$ , requires

C, 60.2; H, 9.72; N, 5.40%

found: a)

C, 60.7; H, 9.85; N, 5.51%

b)

C, 59.75; H, 9.58; N, 5.38%

The IR spectrum (film) of methyl( $\beta$ -carboethoxy-n-propyl)amine (117) showed the ester CO band at  $1730\text{ cm.}^{-1}$ , ester group at  $1200\text{ cm.}^{-1}$  and a broad NH band centred at  $3345\text{ cm.}^{-1}$ , whereas the NMR spectrum ( $\text{CCl}_4$ ) showed the  $\text{N-CH}_3$  singlet at 2.38 p.p.m.,  $\text{C-CH}_3$  doublet centred at 1.14 p.p.m.,  $\text{CH}_2$  quartet of the ethyl ester centred at 4.13 p.p.m. and the  $\text{CH}_3$  triplet of the ethyl ester centred at 1.25 p.p.m.

The IR spectrum (film) of di-( $\beta$ -carboethoxy-n-propyl) methyl amine (118) showed a sharp CO band of the esters at  $1730\text{ cm.}^{-1}$ , a broad band of the esters centred at  $1175\text{ cm.}^{-1}$ ; whereas the NMR spectrum ( $\text{CDCl}_3$ ) showed an  $\text{N-CH}_3$  singlet at 2.24 p.p.m., one pair of overlapping  $\text{C-CH}_3$  doublets centred at 1.12 p.p.m., one pair of superimposed quartets of the  $\text{CH}_2$  of the ethyl esters centred at 4.18 p.p.m. and one pair of overlapping triplets due to the  $\text{CH}_3$  of ethyl esters centred at 1.25 p.p.m.

Methyl( $\beta$ -Carboethoxy-Ethyl)( $\beta$ -Carboethoxy-n-Propyl)Amine (119).

a) Methyl( $\beta$ -carboethoxy-n-propyl)amine (117), (20 g.) and ethyl acrylate (17 g.) were mixed and heated under reflux overnight. The reaction mixture was distilled to give methyl( $\beta$ -carboethoxy-ethyl)( $\beta$ -carboethoxy-n-propyl)amine (29.63 g., 85%) b.p.  $90-92^\circ/0.1\text{ mm.}$

When the two reactants were mixed, kept at room temperature for 4 hours, warmed for 4 hours with occasional shaking and then heated gently under reflux for 15 hours, a yield of 90-95% of the diester was obtained on distillation.

b) Methyl( $\beta$ -carboethoxy-n-propyl)amine (53 g.) was mixed with ethyl acrylate (38 g.) and kept at room temperature for 4-5 days. <sup>71a</sup>

Distillation of the reaction mixture yielded the required amine (119 , 60 g., 81%).

$C_{12}H_{23}O_4N$  requires: C, 58.75; H, 9.45; N, 5.71%

found: C, 58.60; H, 9.46; N, 5.70%

The IR spectrum (film) showed a sharp band due to the CO of the esters at  $1730\text{ cm.}^{-1}$  and a rather broad band due to the esters at  $1180\text{ cm.}^{-1}$ . Whereas the NMR spectrum ( $CDCl_3$ ) showed the  $N-CH_3$  singlet at 2.26 p.p.m., one  $C-CH_3$  doublet centred at 1.12 p.p.m., one pair of superimposed quartets due to the  $CH_2$  of the ethyl esters and one pair of overlapping triplets due to the  $CH_3$  of the ethyl esters, centred at 4.7 p.p.m. and 1.25 p.p.m. respectively.

1:5-Dimethyl-3-Carboethoxy-4-Piperidone (120).

Methyl( $\beta$ -carboethoxyethyl)( $\beta$ -carboethoxy-n-propyl)amine (119) was cyclised under a variety of conditions using NaH/benzene, NaH/xylene and NaOEt/xylene. The basic procedure was the same in all the three cases except that in NaOEt/xylene method, ethanol was distilled off as soon as it was formed in the reaction. However, the best system was found to be NaH/benzene.

A 2 l. flask was fitted with an efficient mechanical stirrer, a reflux condenser, a dropping funnel and a nitrogen inlet tube. The apparatus was flushed with nitrogen and dry benzene (550 ml.) was introduced, sodium hydride (50% dispersion, 30 g.) was then added and the mixture heated gently. When refluxing began, about 3 g. of methyl ( $\beta$ -carboethoxy-ethyl)( $\beta$ -carboethoxy-n-propyl)amine was run into the



flask from the dropping funnel. After 7-10 minutes 2 ml. of absolute ethanol was added. After the vigorous reaction had subsided, the rest of the methyl ( $\beta$ -carboethoxy-ethyl)( $\beta$ -carboethoxy-n-propyl)amine (122.167 g.) in dry benzene (150 ml.) was added dropwise over a period of 2 hours and the refluxing continued for another 3 hours.

The mixture was cooled in an ice-bath and ice-cold water (200 ml.) was added. The aqueous layer was separated and the organic layer extracted with 20% sodium hydroxide solution.

The aqueous extracts were acidified with hydrochloric acid. The solution was then again basified and saturated with sodium carbonate (anhydrous) and extracted several times with ether. Ethereal extracts were dried and ether was removed on the steam bath. The residue was distilled to give 1:5-dimethyl-3-carboethoxy-4-piperidone (79.883 g., 78.5%) b.p.  $68^{\circ}/0.05$  mm.

The yield of the pure keto ester (120) was always 76% or higher.

$C_{10}H_{17}O_3N$  requires: C, 60.28; H, 8.60; N, 7.03%

found: C, 60.1; H, 8.44; N, 7.1%

The IR spectrum (film) exhibited bands of the CO group at  $1622\text{ cm.}^{-1}$ ,  $1660\text{ cm.}^{-1}$ ,  $1720\text{ cm.}^{-1}$  and  $1744\text{ cm.}^{-1}$ . The NMR spectrum ( $CDCl_3$ ) showed the split N-CH<sub>3</sub> singlet centred at 2.42 p.p.m. and the C-CH<sub>3</sub> doublet also gave a complex splitting pattern from 0.95 to 1.3 p.p.m. The ethyl group of the ester showed a quartet due to the CH<sub>2</sub> centred at 4.28 p.p.m. and a triplet due to CH<sub>3</sub> centred at 1.3 p.p.m.

1:3-Dimethyl-4-Piperidone (121).

1:5-Dimethyl-3-carboethoxy-4-piperidone (154 g.) was heated under reflux with hydrochloric acid (30%, 700 ml.) until the solution gave no violet colouration with ferric chloride solution (usually 4-5 hours required). The solution was then cooled, basified, saturated with sodium carbonate (anhydrous) and then extracted several times with ether. Ethereal extracts were dried, ether was removed on the steam bath and the residue was distilled to yield 1:3-dimethyl-4-piperidone (78.951 g., 80%), b.p. 61-62°/12 mm. (lit.<sup>71b</sup> b.p. 62-64°/12 mm.).

The IR spectrum (film) showed the sharp CO band at 1710 cm.<sup>-1</sup>. The NMR spectrum (CDCl<sub>3</sub>) showed the N-CH<sub>3</sub> singlet at 2.4 p.p.m. and the C-CH<sub>3</sub> doublet centred at 1.02 p.p.m.

Pyrrolidine Enamine of 1:3-Dimethyl-4-Piperidone (123).

1:3-Dimethyl-4-piperidone (13.89 g.) was added to pyrrolidine (11.5 g., redistilled) in dry benzene (140 ml.) under nitrogen. After adding a few crystals of toluene-p-sulphonic acid as catalyst, the mixture was heated under reflux on a heating mantle, with a Dean-Stark apparatus fitted to the flask. Heating was continued until no more water appeared in the side arm (about 4 to 5 hours).

Most of the benzene was removed at atmospheric pressure and the residue distilled to give colourless enamine (123) (17.8 g., 85%) b.p. 67-70°/0.4 mm. In several runs the yield was always between 85-90%.

The NMR spectrum ( $\text{CDCl}_3$ ) showed a vinyl hydrogen as a triplet centred at 4.28 p.p.m., the  $\text{N-CH}_3$  singlet at 2.33 p.p.m. and the  $\text{C-CH}_3$  doublet centred at 1.23 p.p.m.

1:3-Dimethyl-5-(Prop-2-ynyl)-4-Piperidone (124).

The enamine (123) of 1:3-dimethyl-4-piperidone (17.5 g.) was dissolved in dry benzene (100 ml.) under nitrogen. Propargyl bromide (21.5 g.) in dry benzene (50 ml.) was added dropwise with stirring in 10 minutes at room temperature. A mildly exothermic reaction occurred and an orange waxy solid began to appear after 5 hours. The stirring continued for 45 hours. The orange complex was decomposed by stirring with water (100 ml.) for 30 minutes at room temperature. The organic layer was separated, washed with water, sodium bicarbonate solution and again with water. The solution was dried and benzene removed under reduced pressure. The residue was chromatographed in petrol-benzene

on Woelm alumina Grade IV to give 1:3-dimethyl-5-(prop-2-ynyl)-4-piperidone (9 g., 60% yield) as a pale yellow oil.

A sample was distilled for analysis.

$C_{10}H_{15}ON$  requires: C, 72.69; H, 9.15; N, 8.48%

found: C, 72.40; H, 9.18; N, 9.03%

The IR spectrum (film) showed a  $C\equiv CH$  band at  $3300\text{ cm.}^{-1}$  and  $CO$  band at  $1705\text{--}1712\text{ cm.}^{-1}$ . The NMR spectrum ( $CDCl_3$ ) showed the methylene group as a sharp doublet centred at 3.37 p.p.m. The acetylenic hydrogen was not clearly resolved. The  $N-CH_3$  singlet appeared at 2.4 p.p.m. and the doublet due to the  $CH_3$  group was centred at 1.09 p.p.m.

The picrate of the compound was an oil which could not be induced to crystallise, the hydrochloride was a hygroscopic solid and the semicarbazone could not be formed.

#### 1:5-Dimethyl-3-Acetonyl-4-Piperidone (125).

This compound was prepared by three different methods.

a) By hydration of 1:3-dimethyl-5-(prop-2-ynyl)-4-piperidone (124).

1:3-Dimethyl-5-(prop-2-ynyl)-4-piperidone (9.72 g.) in absolute methanol (25 ml.) was added dropwise with stirring under nitrogen over 10 minutes to a catalyst solution prepared by warming a mixture of red mercuric oxide (4.0 g.), boron trifluoride etherate (redistilled, 3 ml.), trichloroacetic acid (15 mg.) and absolute methanol (15 ml.). The stirring was continued at room temperature for 3.5 hr. The solution was then filtered from the grey inorganic salts and concentrated under vacuum.

It was then added to sulphuric acid (10%, 100 ml.) and stirred for 20 minutes at 50°. The solution was cooled, made alkaline with dilute ammonia and then extracted with chloroform. The chloroform extracts were dried and evaporated under nitrogen to yield 5.1 g. (50%) of 1:5-dimethyl-3-acetonyl-4-piperidone (125). It was purified by passage through Woelm alumina grade V. A small quantity, on distillation under nitrogen, gave a yellow oil, b.p. 85-8°/0.3 mm. and darkens on standing.

$C_{10}H_{17}O_2N$  requires: C, 65.57; H, 9.29; N, 7.65%

found a): C, 65.9; H, 8.87; N, 7.8%

b): C, 65.6; H, 9.07; N, 7.8%

The IR spectrum (film) showed the CO band at 1715  $cm^{-1}$ . The NMR spectrum ( $CDCl_3$ ) showed a  $CH_3CO$  singlet at 2.2 p.p.m., and  $N-CH_3$  singlet at 2.4 p.p.m. and  $C-CH_3$  doublet centred at 1.05 p.p.m.

The hydrochloride of the compound turns brown, the picrate was an oil and no disemicarbazone could be obtained.

b) By alkylation of the enamine (123) of 1:3-dimethyl-4-piperidone with bromoacetone.

The solution of enamine (15.4 g.) in dry benzene (100 ml.) was cooled thoroughly in an ice-bath and then bromoacetone (12.0 g.) in dry benzene (50 ml.) was added dropwise during 2 hours with vigorous stirring under an atmosphere of nitrogen. An orange oil began to precipitate from the reaction mixture after about 45 minutes. The stirring was continued for

45 hours. The orange enamine complex was then decomposed by stirring with water (75 ml.) for 30 minutes at room temperature. The benzene layer was separated and the aqueous solution was extracted several times with chloroform. The organic extracts were combined, washed with water, sodium bicarbonate solution and again with water. Removal of the solvents under nitrogen gave a dark red oil. It was purified by passing through alumina grade V yielding 10 g. (65%) of 1:5-dimethyl-3-acetonyl-4-piperidone.

- c) By alkylation of the sodium enolate of 1:5-dimethyl 3-carboethoxy-4-piperidone with bromoacetone and subsequent hydrolysis and decarboxylation of the product (128).

1:5-Dimethyl-3-carboethoxy-4-piperidone (39.3 g.) in dry dimethoxyethane (50 ml.) was added dropwise over a period of one hour to a boiling well-stirred suspension of sodium hydride (11 g., 50% dispersion) in dry dimethoxyethane (150 ml.) under nitrogen. The reaction mixture was then heated under reflux for 40 minutes and then allowed to cool. When the reaction mixture attained the room temperature, bromoacetone (30 g.) was added dropwise over a period of 3 hours with vigorous stirring. The stirring was continued for 24 hours and then heated gently for 0.5 hours and then allowed to cool. The sodium bromide formed during the reaction was dissolved by the addition of cold water (250 ml.) and the reaction mixture was extracted several times with chloroform. The organic

solution was, in turn, extracted several times with 3N hydrochloric acid. The acid extracts were made alkaline, saturated with anhydrous sodium carbonate and extracted with ether. The ether extracts were dried and evaporated to yield 34.6 g. (69%) of almost pure 1:5-dimethyl-3-acetonyl 3-carboethoxy-4-piperidone. It was purified by chromatography on Woelm alumina grade IV using a mixture of petrol and benzene (10:90). A small quantity was distilled under nitrogen as a pale yellow oil (b.p.  $100^{\circ} / 5.9 \times 10^{-4}$ ) which darkens in air.

$C_{13}H_{21}O_4N$  requires: C, 61.17; H, 8.24; N, 5.49%

found: C, 61.1; H, 8.04; N, 5.6%

The IR spectrum (film) showed a broad band from  $1715\text{ cm}^{-1}$  to  $1745\text{ cm}^{-1}$  due to three C=O groups. The NMR spectrum ( $CDCl_3$ ) showed a CO-CH<sub>3</sub> singlet at 2.23 p.p.m., an N-CH<sub>3</sub> singlet at 2.35 p.p.m., a C-CH<sub>3</sub> doublet centred at 4.3 p.p.m., and a triplet due to the CH<sub>3</sub> of the ethyl ester centred at 1.3 p.p.m. The quartet and the triplet due to the CH<sub>2</sub> and CH<sub>3</sub> groups respectively of the ethyl ester showed a shoulder on each of the peaks indicating the presence of epimers (128a and b).

The preceding 1:5-dimethyl-3-acetonyl-3-carboethoxy-4-piperidone (16.188 g.) was heated under reflux with hydrochloric acid (30%, 400 ml.) for 3-4 hours, in an atmosphere of nitrogen. The reaction mixture was cooled in an ice-bath and washed several times with chloroform. The acid solution was then basified with dilute ammonia or anhydrous sodium carbonate and extracted with chloroform. The organic extracts were dried

and evaporated. The residue was taken up in benzene and passed rapidly through alumina grade V yielding, on evaporation of the solvent, 5.839 g. (50%) of 1:5-dimethyl-3-acetonyl-4-piperidone.



Attempted Preparation of 2:4-Dimethyl-1:2:3:4:7:7a-Hexahydro-6H-2-Pyrindin-6-one (137).

a) The diketone (1.83 g.) was dissolved in dry tertiary-butanol (15 ml.) and added at room temperature to a solution of potassium (0.39 g.) in dry tertiary butanol (15 ml.), under nitrogen. The solution became dark red in colour and was stirred for 30 minutes and was then poured into ice-cold hydrochloric acid (5%, 100 ml.). The acid solution was washed with chloroform, it was then made alkaline with dilute ammonia and extracted with chloroform. Drying and removal of the solvent under reduced pressure gave the starting material as evident by NMR and IR spectra.

b) Using the same quantities of the diketone, dry tertiary butanol and potassium as in (a), the reaction mixture was heated under reflux for 0.5 hours in one experiment and one hour in the other experiment and then worked up as before producing a black residue which was found to be the starting material by NMR spectrum.

c) The diketone (4.0 g.) was mixed with the boiling water (250 ml.) under nitrogen. The solution was heated under reflux and stirred vigorously while sodium hydroxide or potassium hydroxide (2%, 45 ml.) was added during 15 minutes. The diketone did not dissolve. This was heated under reflux for 6 hours. After cooling, it was extracted with chloroform. The organic extracts dried and evaporated yielding a black residue containing a small quantity of the starting material.

d) The diketone was dissolved in absolute methanol and heated with a solution of sodium in methanol. After working up as usual, the starting material was recovered.

e) The diketone (3.5 g.) was dissolved in a solution of concentrated hydrochloric acid (50 ml.) glacial acetic acid (100 ml.) and water (4 ml.). This solution was then refluxed for 36 hours under nitrogen. After cooling, the acid solution was washed with chloroform and then concentrated under vacuum. The concentrate was basified with dilute ammonia and extracted with chloroform. Drying and evaporation of the solvent furnished the starting material as thick dark red oil.

Ethyl- $\gamma$ -Bromo Acetoacetate

This was prepared by the method of Toan and Tefas.<sup>91</sup>

1:5-Dimethyl-3-(3'-Carboethoxy-Acetyl)-4-Piperidone (138).

The enamine (37.548 g.) of 1:3-dimethyl-4-piperidone was dissolved in dry benzene (50 ml.) under nitrogen with cooling in an ice-bath. Ethyl- $\gamma$ -bromoacetoacetate (48 g.) in dry benzene (100 ml.) was added dropwise with stirring over a period of 3 hours. The reaction mixture became dark red in colour and a waxy compound began to deposit along the sides after one hour. The stirring was continued for 65 hours at room temperature. The enamine complex was then decomposed by stirring with cold water (100 ml.) for 30 minutes at room temperature. The benzene layer was separated and the aqueous layer was extracted several times with chloroform. The organic extracts were dried and the solvent removed under reduced pressure yielding 36.290 g. of 1:5-dimethyl-3-(3'-carboethoxy acetyl)-4-piperidone. This was purified by passing through Woelm alumina grade IV using benzene as the eluent.

$C_{13}H_{21}O_4N$  requires: C, 61.17; H, 8.24; N, 5.49%

found: C, 61.0; H, 8.11; N, 5.6%

The IR spectrum (film) of the compound showed a broad band centred at 1720  $cm^{-1}$  due to the three carbonyl functions. The NMR spectrum ( $CDCl_3$ ) showed the  $C-CH_3$  doublet centred at 1.02 p.p.m., the  $N-CH_3$  singlet at 2.4 p.p.m., the

CH<sub>3</sub> triplet of the ethyl ester centred at 1.28 p.p.m., the CH<sub>2</sub> quartet of the ethyl ester centred at 4.28 p.p.m., and the CH<sub>2</sub> singlet between the keto and the ester group of the side-chain at 2.49 p.p.m. The CH<sub>2</sub> singlet between the keto and the ester groups disappeared when the solution in CDCl<sub>3</sub> was shaken with a drop of D<sub>2</sub>O.

2:4-Dimethyl-5-Carboethoxy-1:2:3:4:5:7-Hexahydro-6H-2-Pyridin-2-one (141).

The preceding compound (6 g.) was dissolved in ether (10 ml.) and then added dropwise to well-stirred concentrated sulphuric acid (20 ml.) which was cooled in acetone-solid carbon dioxide bath. The stirring was continued for 4 hours. The acid solution was poured into ice and washed with chloroform to remove any organic impurities. The solution was then made basic with aqueous ammonia (1:1) and extracted with chloroform. The chloroform extracts were dried and evaporated under reduced pressure to yield 3.315 g. of 2:4-dimethyl-5-carboethoxy-1:2:3:4:5:7-hexahydro-6H-2-pyridin-2-one and was purified by chromatography on Woelm alumina grade IV. A consistent analysis on the carbon of the compound could not be obtained after distillation, indicating that the compound is undergoing decomposition on distillation, and the compound did not form a solid derivative as well.

C<sub>13</sub>H<sub>19</sub>O<sub>3</sub>N requires: C, 65.80; H, 8.07; N, 5.90%

found: C, 64.13; H, 8.25; N, 5.75%

The IR spectrum (film) showed a broad band from 1705 cm.<sup>-1</sup> to 1715 cm.<sup>-1</sup>

due to the carbonyl functions, a broad bulge from 1615 to 1625  $\text{cm}^{-1}$  due to an unconjugated  $\text{C}=\text{O}$ . The NMR spectrum ( $\text{CDCl}_3$ ) showed no vinyl hydrogen, the  $\text{C}-\text{CH}_3$  doublet was centred at 1.02 p.p.m., the  $\text{N}-\text{CH}_3$  singlet at 2.4 p.p.m., the  $\text{CH}_2$  quartet of the ethyl ester centred at 4.28 p.p.m. and the  $\text{CH}_3$  triplet of the ethyl ester centred at 1.28 p.p.m., but the singlet due to the  $\text{CH}_2$  group between the two carbonyls had disappeared.

2:4-Dimethyl-1:2:3:4:5:7-Hexahydro-6H-2-Pyridin-2-one (142).

The above bicyclic  $\beta$ : $\gamma$ -unsaturated ketone (3 g.) was dissolved in hydrochloric acid (30%, 50 ml.) and heated under reflux in an atmosphere of nitrogen for 2.5 hours. The solution was cooled and washed with chloroform. The acid solution was then made alkaline with aqueous ammonia (1.1) and extracted with chloroform. The organic extracts, on drying and evaporation yielded 1.1 g. of 2:4-dimethyl-1:2:3:4:5:7-hexahydro-6H-2-pyridin-2-one and was purified by chromatography on Woelm alumina grade V in benzene.

$\text{C}_{10}\text{H}_{15}\text{ON}$  requires: C, 72.69; H, 9.15; N, 8.48%

found: C, 72.5; H, 9.18; N, 8.55%

The IR spectrum ( $\text{CHCl}_3$ ) showed a band at 1705  $\text{cm}^{-1}$  due to the carbonyl function and a broad bulge from 1605 to 1625  $\text{cm}^{-1}$  due to an unconjugated  $\text{C}=\text{C}$ . The NMR spectrum showed a  $\text{C}-\text{CH}_3$  doublet centred at 1.0 p.p.m. and an  $\text{N}-\text{CH}_3$  singlet at 2.4 p.p.m.

1:5-Dimethyl-3-(1'-methyl-acetonyl)-4-piperidone (143).

This was also prepared by two procedures.

- a) By alkylation of the enamine (123) of 1:3-dimethyl-4-piperidone with 3-bromo-2-butanone.

The pyrrolidine enamine (123, 14.555 g.) was dissolved in dry benzene under nitrogen and cooled in an ice-bath. To this solution 3-bromo-2-butanone (14.00 g.) was added dropwise over a period of 1.5 hours with ice-bath cooling. The mixture was stirred at room temperature for 45 hours. The reaction mixture was stirred for another 4 hours at about 40-50°. Water (100 ml.) was added to decompose the enamine complex and extracted with chloroform. The chloroform extracts were dried and evaporated to give 7.96 g., 50%, of the residue. A small quantity was distilled for analysis as a pale oil darkening on standing, b.p. 51-2°/0.1 mm.

$C_{11}H_{19}O_2N$  requires: C, 66.97; H, 9.71; N, 7.10%

found: C, 66.86; H, 9.51; N, 7.01%

The IR spectrum (film) showed the C=O band at 1712  $cm^{-1}$  due to the two carbonyl functions. The NMR spectrum ( $CDCl_3$ ) showed a pair of C-CH<sub>3</sub> doublets centred at 0.96 p.p.m. and 0.98 p.p.m., the N-CH<sub>3</sub> singlet and the CO-CH<sub>3</sub> singlet were superimposed at 2.3 p.p.m.

- b) By alkylation of the enolate anion of 1:5-dimethyl-3-carboethoxy-4-piperidone (120) with 3-bromo-2-butanone and subsequent hydrolysis of the product (144).

1:5-Dimethyl-3-carboethoxy-4-piperidone (20, 15 g.) in dry dimethoxy-ethane (15 ml.) was added dropwise to a boiling suspension of sodium hydride (50% dispersion, 4 g.) in dry dimethoxyethane (100 ml.) with stirring under nitrogen. The mixture was refluxed for 1.5 hours. The reaction mixture was cooled and 3-bromo-2-butanone (11.7 g.) in dry dimethoxy-ethane (25 ml.) was added dropwise, stirred for 24 hours and then heated under reflux for 0.5 hours. Sodium bromide formed was dissolved by the addition of water (50 ml.) and the reaction mixture was extracted with chloroform. The chloroform solution was then extracted several times with 10% hydrochloric acid. The acid solution was made alkaline and extracted again with chloroform. The chloroform extracts were dried and evaporated under reduced pressure. The residue was purified by chromatography in benzene on Woelm alumina grade IV yielding 9.81 g. (50%) of the required product. A small quantity was distilled for analysis as a yellow oil darkening on standing, b.p.  $86^{\circ}/1.47 \times 10^{-4}$ .

$C_{14}H_{23}O_4N$  requires: C, 62.45; H, 8.55; N, 5.2%

found: C, 62.3; H, 8.45; N, 5.4%

The IR spectrum (film) showed the presence of the C=O band at  $1720\text{ cm.}^{-1}$  due to the three carbonyl functions. The NMR spectrum ( $CDCl_3$ ) showed CO-CH<sub>3</sub> singlet at 2.3 p.p.m., an N-CH<sub>3</sub> singlet at 2.4 p.p.m.,

the ester  $\text{CH}_2$  quartet centred at 4.35 p.p.m., the ester  $\text{CH}_3$  triplet as well as the two  $\text{C}-\text{CH}_3$  doublets formed a rather complex splitting pattern from 0.95 p.p.m. to 1.5 p.p.m. Each of the  $\text{CO}-\text{CH}_3$  and  $\text{N}-\text{CH}_3$  singlets was split further indicating the presence of the epimeric forms (144a and 144b).

The preceding carboethoxy-compound (144, 8 g.) was dissolved in 30% hydrochloric acid (100 ml.) and heated under reflux for 4 hours in an atmosphere of nitrogen. Excess of water and hydrochloric acid were removed under reduced pressure. The hydrochloride of the compound was basified with ammonia (1:1) and the base extracted with chloroform. The chloroform extracts were dried and evaporated to yield 2.9 g. (50%) of the product. The residue was distilled giving a pale-yellow liquid, b.p.  $51-2^\circ/0.1$  mm. darkening on standing.

The two  $\text{C}-\text{CH}_3$  doublets gave a complex splitting pattern in the NMR spectrum. All attempts to equilibrate the compound to one isomer failed.

Attempted Cyclodehydration of 1:5-Dimethyl-3-(1'-methyl acetyl)-4-piperidone (143).

The product obtained by the alkylation of the pyrrolidine enamine (123) was used for cyclodehydration reactions. All those reactions used for the cyclodehydration of 1:5-dimethyl-3-acetyl-4-piperidone (125), when employed in this case, failed.

Di-( $\beta$ -carbomethoxy-ethyl)-phenyl-amine (145).

A mixture of aniline (93 g.), methyl acrylate (230 g.) glacial



acetic acid (144 g.) and cuprous chloride (19 g.) was heated under reflux with stirring in an atmosphere of nitrogen for 28 hours. The cold mixture was dissolved in ether (400 ml.) washed with water (3 x 300 ml.), then with aqueous ammonia (1:1; 3 x 300 ml.) and dried. Ether was removed on the steam-bath whereas the unreacted aniline and methyl acrylate were removed under reduced pressure.

The residue was distilled yielding 3 g. of phenyl- $\beta$ -carbomethoxy-ethyl-amine (146), b.p. 95-95°/0.1 mm. (lit.<sup>71a</sup> b.p. 125-6°/ 3 mm.) and 160 g. (60%) of di-( $\beta$ -carbomethoxy-ethyl)-phenyl-amine (145), b.p. 134-138°/0.1 mm.

$C_{14}H_{19}O_4N$  (145) requires: C, 63.38; H, 7.22; N, 5.28%

found: C, 63.8; H, 7.10; N, 5.48%

N-Phenyl-3-carbomethoxy-4-piperidone (147).

Di-( $\beta$ -carbomethoxy-ethyl)-phenyl-amine (108 g.) was cyclised using sodium hydride (50% dispersion; 25 g.) in dry benzene under nitrogen. The details of the procedure were the same as those for the cyclisation of ( $\beta$ -carboethoxy-n-propyl)( $\beta$ -carboethoxy-ethyl)methyl-amine (119), the yield of the compound (147) was 76 g. (80%). N-Phenyl-3-carbomethoxy-4-piperidone, being unstable to distillation, was characterised as the ethylene ketal, b.p. 158-160°/0.2 mm.

$C_{15}H_{19}O_4N$  requires: C, 64.96; H, 6.91; N, 5.05%

found a): C, 65.5; H, 6.94; N, 5.2%

b): C, 65.9; H, 7.04; N, 5.2%

N-Phenyl-4-piperidone (148).

A solution of N-phenyl-3-carbomethoxy-4-piperidone (30 g.) in hydrochloric acid (20%, 150 ml.) was heated under reflux with stirring in an atmosphere of nitrogen. The reaction mixture was concentrated in vacuo to 30 ml., cooled, basified and extracted with chloroform. The chloroform extracts were dried and the solvent was removed under reduced pressure. Distillation of the residue under nitrogen afforded 15.752 g. (70%) of N-phenyl-4-piperidone b.p. 108-10<sup>0</sup>/0.05 mm. (lit.<sup>75</sup> b.p. 112<sup>0</sup>/0.5 mm.).

Attempted preparation of 3-acetonyl-N-phenyl-4-piperidone (150).

N-Phenyl-4-piperidone (8.75 g.) was converted into the pyrrolidine enamine (149) by heating with pyrrolidine (9 g.) in dry benzene (150 ml.) by the same procedure as described before. The enamine (149) could not be purified and was used as such after the addition of sufficient sodium bicarbonate. The alkylation with bromoacetone (6.85 g.) was carried out as before. The residue was purified by chromatography on alumina grade V in benzene. The benzene solution on evaporation, gave 5.1 g. of a dark brown residue. The IR spectrum (film) showed a CO band at 1735 cm.<sup>-1</sup> and a sharp band at 1625 cm.<sup>-1</sup> and the mono-substituted benzene at 725 cm.<sup>-1</sup> and 785 cm.<sup>-1</sup>. The NMR spectrum (CDCl<sub>3</sub>) showed a 3-proton singlet (COCH<sub>3</sub>) at 2.25 p.p.m., a 2-proton doublet centred at 4.1 p.p.m. and 9 protons in the aromatic region.

Methyl( $\beta$ -cyano-ethyl)amine (158).

This was prepared by the method of Cook and Reed.<sup>76</sup>

Di-( $\beta$ -cyano-ethyl)methylamine (159).

This was prepared by two procedures.

a) Methyl( $\beta$ -cyano-ethyl)amine (120 g.) was mixed with acrylonitrile (95 g.) and heated under reflux for 24 hours. The unreacted acrylonitrile was removed under reduced pressure on the steam bath. The residue was distilled to give 170 g. (86%) of di-( $\beta$ -cyanoethyl)-methylamine, b.p.  $118^{\circ}/0.2$  mm. (lit. b.p.  $133^{\circ}/5$  mm.).<sup>76</sup>

b) Acrylonitrile (79 g.) was added dropwise with stirring to an ethanolic solution of methylamine (33%, 50 ml.) surrounded by an acetone-carbon dioxide bath. The solution was allowed to stand at room temperature for a week or longer. The unreacted acrylonitrile and ethanol were removed under reduced pressure. The residue was distilled to give 55 g. (80%) of di-( $\beta$ -cyano-ethyl)methylamine, b.p.  $118^{\circ}/0.2$  mm.

Di-( $\beta$ -carboethoxy-ethyl)methylamine (160).

Di-( $\beta$ -cyanoethyl)methyl amine (127 g.) was dissolved in absolute ethanol (600 ml.) and saturated with hydrogen chloride gas. Much heat was evolved and crystals began to appear. Saturation was completed in about one hour. The mixture was warmed gently for another hour. It was then cooled, dissolved in water, saturated with anhydrous sodium carbonate and extracted with ether. The ether extracts were dried and

the solvent was removed on the steam bath. Distillation of the residue afforded 172 g. (80%) of di-( $\beta$ -carboethoxy-ethyl)methyl amine, b.p. 95-100°/0.1 mm. (lit.<sup>66b</sup>, b.p. 118-9°/0.5 mm., and b.p.<sup>66a</sup> 136-8°/4 mm.).

N-Methyl-3-carboethoxy-4-piperidone (161).

Di-( $\beta$ -carboethoxy-ethyl)methyl-amine (148.5 g.) in dry benzene (150 ml.) was cyclised using sodium hydride (50% dispersion, 34 g.) in dry benzene (600 ml.). The rest of the details of the procedure were the same as those reported for the cyclisation of methyl( $\beta$ -carboethoxy)-n-propyl( $\beta$ -carboethoxy-ethyl)amine (119). The yield of the keto ester (161) was 85 g. (72%), b.p. 75-80°/0.1 mm. (lit.<sup>66a</sup> b.p. 114-116°/4 mm.).

Ethylene ketal (164) of N-methyl-3-carboethoxy-4-piperidone.

3-Carboethoxy-N-methyl-4-piperidone (44.612 g.) was dissolved in ethylene glycol (90 ml.) and saturated with hydrogen chloride gas with ice-bath cooling. It was then heated at 65-75° in an oil bath for one hour with stirring, cooled and left overnight at room temperature. Next day, the solution was poured into crushed ice, saturated with anhydrous sodium carbonate and extracted with ether. The ether extracts were dried and the solvent was removed on the steam bath. The residue (54.5 g., quantitative yield) was distilled, yielding 35 g. (65%) of the ketal, b.p. 90-110°/0.2 mm. A constant boiling fraction was submitted for analysis.

$C_{11}H_{19}O_4N$  requires: C, 57.62; H, 8.35; N, 6.11%  
(b.p. 100°/0.2 mm) found: C, 57.8; H, 8.36; N, 6.3%

Because of this considerable loss on distillation, it was decided to use the crude ketal for the next step.

The IR spectrum (film) showed a rather broad ester C=O band at  $1730\text{ cm.}^{-1}$ . The NMR spectrum ( $\text{CDCl}_3$ ) showed the 4-proton ethylene ketal singlet at 4.00 p.p.m., the N- $\text{CH}_3$  singlet at 2.3 p.p.m., ester  $\text{CH}_2$  quartet centred at 4.22 p.p.m. and the ester  $\text{CH}_3$  triplet centred at 1.29 p.p.m.

Ethylene ketal (165) of N-methyl-3-hydroxymethyl-4-piperidone.

The crude ketal (39.612 g.) of N-methyl-3-carboethoxy-4-piperidone in dry ether (300 ml.) was added with stirring to a suspension of lithium aluminium hydride (5 g.) in dry ether at room temperature. The addition was so regulated as to keep the reaction mixture refluxing gently. After the addition was complete, the reaction mixture was heated under reflux for 5 hours, and then cooled in a bath of crushed ice. The excess lithium aluminium hydride was destroyed by the cautious addition of ethyl acetate. The insoluble salts were dissolved carefully in ice-cold sulphuric acid (10%, 800 ml.). The organic layer was separated, the acid solution was made alkaline, saturated with anhydrous sodium carbonate and extracted with chloroform several times. The chloroform extracts were dried, and the solvent was removed under reduced pressure. The liquid residue crystallised on standing and was recrystallised from petrol (60-80°) yielding 30.5 g. (94%) of the alcohol, m.p. 86-7°.

Two recrystallisations from petrol furnished the analytical sample.

$\text{C}_9\text{H}_{17}\text{O}_3\text{N}$  requires: C, 57.73; H, 9.15; N, 7.5%

found: C, 58.2; H, 9.37; N, 7.5%

The IR spectrum (Nujol) showed a broad OH band in the region 3100 to 3400  $\text{cm}^{-1}$ . The NMR spectrum ( $\text{CDCl}_3$ ) showed the ethylene ketal protons as a singlet at 4.05 p.p.m., the  $\text{N-CH}_3$  singlet at 2.33 p.p.m. On shaking with a drop of  $\text{D}_2\text{O}$ , exchange of the OH proton occurred.

Ethylene ketal (166) of N-methyl-3-chloromethyl-4-piperidone.

The ketal (18.7 g.) of N-methyl-3-hydroxymethyl-4-piperidone was dissolved in chloroform (100 ml.). The solution was saturated with hydrogen chloride gas at room temperature. To this solution was added with stirring, pure thionyl chloride (18.0 g.) so as to keep the solution refluxing gently. After the addition was complete, the reaction mixture was heated under reflux for one hour. Excess of thionyl chloride and chloroform was removed under reduced pressure. The residue was diluted with water, saturated with anhydrous sodium carbonate and extracted with ether. The ethereal extracts were dried and the solvent was removed on the steam bath. The residue was distilled to give the colourless ketal (16.6 g., 80%) of N-methyl-3-chloromethyl-4-piperidone, b.p.  $82-4^\circ/0.2 \text{ mm.}$

$\text{C}_9\text{H}_{16}\text{O}_2\text{NCl}$  requires: C, 52.56; H, 7.79; N, 6.81%

found: C, 53.1; H, 7.70; N, 6.9%

The IR spectrum (film) showed a sharp C-Cl band at  $720 \text{ cm}^{-1}$ . The NMR spectrum ( $\text{CDCl}_3$ ) showed ethylene ketal singlet at 4.00 p.p.m., the  $\text{N-CH}_3$  singlet at 2.32 p.p.m. and there was no exchange on shaking with  $\text{D}_2\text{O}$ .

Ethylene ketal (167) of N-methyl-3-cyanomethyl-4-piperidone.

The ketal (10.27 g.) of N-methyl-3-chloro-methyl-4-piperidone in dry dimethyl sulphoxide (50 ml.) was added dropwise to a well-stirred suspension of sodium cyanide (7.5 g.) in dry dimethyl sulphoxide (100 ml.) at  $110^{\circ}$  (oil bath temperature). After the addition was complete, the temperature was raised and maintained between  $135-140^{\circ}$  for 3 hours. The reaction mixture was cooled, poured in a beaker of crushed ice and extracted with 10% hydrochloric acid. The acid solution was made alkaline, saturated with anhydrous sodium carbonate and extracted with ether. The ethereal extracts were dried and the ether was taken off on the steam bath. The residue was distilled to give the colourless cyanoketal (6.9 g., 70%) b.p.  $110-2^{\circ}/0.3$  mm.

$C_{10}H_{16}O_2N_2$  requires: C, 61.20; H, 8.22; N, 14.28%

found: C, 61.00; H, 8.12; N, 14.3%

The IR spectrum (film) showed a sharp CN band at  $2220\text{ cm.}^{-1}$ . The NMR spectrum ( $CDCl_3$ ) showed the ethylene ketal as a singlet at 4.02 p.p.m. and the  $N-CH_3$  singlet at 2.32 p.p.m.

Ethylene ketal (168) of N-methyl-3-carboethoxy-methyl-4-piperidone.

The ketal (3.92 g.) of N-methyl-3-cyanomethyl-4-piperidone was dissolved in absolute ethanol (60 ml.), and saturated with hydrogen chloride gas. The saturated solution was heated under reflux for one hour. It was then cooled, diluted with water, basified, saturated with

anhydrous sodium carbonate and extracted with ether. Ethereal extracts were dried and the solvent was removed on the steam bath. The residue was distilled to give 3.8 g. (80%) of the ketal of N-methyl-3-carboethoxymethyl-4-piperidone, b.p.  $92-5^{\circ}/0.2$  mm.

$C_{12}H_{21}O_4N$  requires: C, 59.24; H, 8.70; N, 5.76%

found: C, 58.6; H, 8.60; N, 5.9%

The IR spectrum (film) showed the  $C=O$  band at  $1720\text{ cm.}^{-1}$  due to the ester carbonyl function and the complete disappearance of CN band. The NMR spectrum ( $CDCl_3$ ) showed the ester  $CH_2$  quartet centred at 4.22 p.p.m., the ester  $CH_3$  triplet centred at 1.25 p.p.m., the  $N-CH_3$  singlet at 2.32 p.p.m. and the ethylene ketal singlet at 4.03 p.p.m.

Ethylene ketal (169) of 1:5-dimethyl-3-carboethoxy-4-piperidone.

1:5-Dimethyl-3-carboethoxy-4-piperidone (44.612 g.) when treated with ethylene glycol (150 ml.) under the same conditions as those described for the preparation of the ethylene ketal (164) of N-methyl-3-carboethoxy-4-piperidone, gave a quantitative yield (54.5 g.) of the ethylene ketal (169) of 1:5-dimethyl-3-carboethoxy-4-piperidone. A considerable quantity was lost on distillation of the ketal, b.p.  $94-110^{\circ}/0.2$  mm., so it was decided to use the crude compound for the next step. A constant boiling fraction, b.p.  $94-5^{\circ}/0.2$  mm. was submitted for analysis.

$C_{12}H_{21}O_4N$  requires: C, 59.24; H, 8.70; N, 5.76%

found: C, 58.9; H, 8.64; N, 5.8%



The IR spectrum (film) showed a rather broad ester C=O band at  $1740\text{ cm}^{-1}$ . The NMR spectrum ( $\text{CDCl}_3$ ) showed the ethylene ketal protons as a singlet at 4.04 p.p.m., an  $\text{N-CH}_3$  singlet at 2.25 p.p.m., the ester  $\text{CH}_2$  quartet centred at 4.26 p.p.m., the ester  $\text{CH}_3$  triplet centred at 1.28 p.p.m. and the  $\text{C-CH}_3$  doublet centred at 0.95 p.p.m.

Ethylene ketal (170) of 1:5-dimethyl-3-hydroxymethyl-4-piperidone.

The preceding carboethoxy-ketal (37.75 g., crude) in dry ether (75 ml.) was reduced with lithium aluminium hydride (3.8 g.) in dry ether (400 ml.). The rest of the details were the same as those reported for the reduction of the ketal (164) of N-methyl-3-carboethoxy-4-piperidone except that the compound was extracted with ether instead of chloroform. The crude solid was recrystallised from petrol (b.p.  $40-60^\circ$ ) furnishing 21.6 g. (69%) of the pure hydroxy-compound (170) m.p.  $76-7^\circ$ .

$\text{C}_{10}\text{H}_{19}\text{O}_3\text{N}$  requires: C, 59.67; H, 9.52; N, 6.96%

found: C, 59.90; H, 9.59; N, 7.00%

The IR spectrum (Nujol) showed a broad OH band from  $3100\text{ cm}^{-1}$  to  $3300\text{ cm}^{-1}$ . The NMR spectrum ( $\text{CDCl}_3$ ) showed the ethylene ketal singlet at 4.02 p.p.m., the  $\text{CH}_2$  doublet of the 3-hydroxy-methyl group centred at 3.92 p.p.m., an  $\text{N-CH}_3$  singlet at 2.25 p.p.m. and the  $\text{C-CH}_3$  doublet centred at 0.9 p.p.m. The hydroxyl proton was present as rather a broad peak at 4.42 p.p.m. which disappeared on shaking the solution with  $\text{D}_2\text{O}$ .

Ethylene ketal (171) of 1:5-dimethyl-3-chloromethyl-4-piperidone.

The alcohol (170, 22.316 g.) was converted into the corresponding chloro-compound (171) by reaction with thionyl chloride (20.15 g.). The procedure used was the same as that used for the conversion of the alcohol (165) to the corresponding chloro-compound (166). The yield of the ketal (171) of 1:5-dimethyl-3-chloromethyl-4-piperidone was 21.76 g. (90%), b.p.  $64-6^{\circ}/0.2$  mm.

$C_{10}H_{18}O_2NCl$  requires: C, 54.67; H, 8.20; N, 6.38%

found: C, 54.80; H, 8.39; N, 6.4%

$C_{10}H_{18}O_2NCl$  picrate (m.p.  $145-6^{\circ}$ ) requires: C, 42.8; H, 4.68; N, 12.49%

found: C, 42.6; H, 4.66; N, 12.40%

The IR spectrum (film) showed the sharp C-Cl band at  $740\text{ cm.}^{-1}$ .

The NMR spectrum ( $CDCl_3$ ) showed the presence of the ethylene ketal singlet at 4.01 p.p.m., the  $CH_2$  doublet of the 3-chloromethyl group centred at 3.78 p.p.m., an N- $CH_3$  singlet at 2.28 p.p.m., the C- $CH_3$  doublet centred at 0.88 p.p.m.

Ethylene ketal (172) of 1:5-dimethyl-3-cyanomethyl-4-piperidone.

The preceding chloro-compound (171; 18 g.), in dry dimethyl sulphoxide (100 ml.) was added to a sodium cyanide (6.5 g.) suspension in dry dimethyl sulphoxide (120 ml.) at  $110^{\circ}$ . The reaction was carried out under the same conditions as those described for the preparation of

N-methyl-3-cyanomethyl-4-piperidone (167) from the corresponding chloro-compound (166). The yield of the ethylene ketal (172) of 1:5-dimethyl-3-cyanomethyl-4-piperidone was 13.7 g. (80%), b.p.  $104-8^{\circ}/0.3$  mm. The compound was characterised as the picrate, m.p.  $158-9^{\circ}$ .

$C_{11}H_{18}O_2N_2$ .picrate requires: C, 46.47; H, 4.78; N, 15.95%

found: C, 46.3; H, 4.70; N, 15.90%

The IR spectrum (film) showed the sharp CN band at  $2245\text{ cm.}^{-1}$ . The NMR spectrum ( $CDCl_3$ ) showed the ethylene ketal singlet at 4.04 p.p.m., an  $N-CH_3$  singlet at 2.29 p.p.m., the  $C-CH_3$  doublet centred at 0.92 p.p.m.

1:5-Dimethyl-3-cyanomethyl-4-piperidone (151).

The ketal (172; 12 g.) of 1:5-dimethyl-3-cyanomethyl-4-piperidone was dissolved in hydrochloric acid (12%, 1000-1200 ml.). This acid solution was heated, either under reflux for 4 hours or on the steam bath for 8-9 hours, with stirring. The solution was cooled, basified, saturated with anhydrous sodium carbonate and extracted with ether. The ethereal extracts were dried and the ether was evaporated on the steam bath. The residue was distilled affording 7.1 g. (60%) of 1:5-dimethyl-3-cyanomethyl-4-piperidone (151), b.p.  $62-4^{\circ}/0.05$  mm. The compound was characterised as the picrate, m.p.  $218-9^{\circ}$ .

$C_9H_{14}ON_2$ .picrate requires: C, 45.57; H, 4.30; N, 17.72%

found: C, 45.6; H, 4.29; N, 17.7%

The IR spectrum (film) showed the sharp CN band at  $2250\text{ cm.}^{-1}$  and the CO band at  $1715\text{ cm.}^{-1}$ . The NMR spectrum ( $\text{CDCl}_3$ ) showed a  $\text{C-CH}_3$  doublet centred at 1.02 p.p.m.

Attempted preparation of 1:5-Dimethyl-3-cyanomethyl-4-hydroxy-4-carboethoxymethyl-piperidine (152).

To granulated zinc (2.5 g.) and iodine (0.07 g.) in a mixture of dry benzene (25 ml.) and dry ether (25 ml.), was added 1:5-dimethyl-3-cyanomethyl-4-piperidone (1.5 g.) and ethyl bromoacetate (1.5 g.). Five additions of zinc (2.5 g.) and a trace of iodine were made at 45-minute intervals and an additional amount of ethyl bromoacetate (1.5 g.) was introduced after 1.5 hours. The mixture was refluxed for a total of 4 hours with occasional vigorous shaking. The residue was dissolved by adding a little acetic acid and methanol and the solution was decanted from zinc into water. Hydrochloric acid (10%, 50 ml.) was added to the solution. The organic layer was separated and the acid solution was washed with ether several times. The acid solution was made alkaline, saturated with anhydrous sodium carbonate and extracted with chloroform. The chloroform extracts were dried and the solvent was removed under reduced pressure. The residue (1.35 g.) was found to be the unchanged starting material from IR and NMR spectra.

Attempted condensation of 1:5-dimethyl-3-cyanomethyl-4-piperidone (151)  
with ethyl cyano-acetate.

1:5-Dimethyl-3-cyanomethyl-4-piperidone (3.32 g.) was heated under reflux with ethyl cyanoacetate (3 g.) in dry benzene containing ammonium acetate or piperidine. The apparatus was fitted with Dean-Stark apparatus. No water separation occurred in 24 to 72 hours. The solvent was removed under reduced pressure. The residue was diluted with water and extracted with ether. The organic solution was then extracted with 10% hydrochloric acid. The acid solution was basified and extracted with ether. Evaporation of the solvent on the steam-bath afforded 2.99 g. of the unchanged starting material as evident by IR and NMR spectra.

1:5-Dimethyl-3-cyanomethyl-4-hydroxy-piperidine (174).

1:5-Dimethyl-3-cyanomethyl-4-piperidone (10 g.) was dissolved in methanol (100 ml.) and cooled to 0°. To this solution, sodium borohydride (1.24 g.) was added with stirring in portions over a period of 10 minutes. The solution was stirred for another hour. It was then poured into a beaker of crushed ice and extracted with chloroform. The chloroform extracts were dried and the solvent was removed under reduced pressure. The residue (8.12 g., 80%) solidified on standing. It was recrystallised from a mixture of benzene and petrol, m.p. 143-6°.

$C_9H_{16}ON_2$  requires: C, 64.25; H, 9.59; N, 16.65%

found: C, 64.5; H, 9.63; N, 16.7%

The IR spectrum (film) showed a broad OH band from 3100-3500  $\text{cm}^{-1}$ , and the CN band at 2260  $\text{cm}^{-1}$ . The NMR spectrum ( $\text{CDCl}_3$ ) showed an  $\text{N-CH}_3$  singlet at 2.33 p.p.m., and the  $\text{C-CH}_3$  doublet appeared as a complex splitting pattern possibly due to the presence of isomeric forms (174a and 174b).

Attempted preparation of the tosylate (175) of 1:5-dimethyl-3-cyanomethyl-4-hydroxy-piperidine.

The preceding secondary alcohol (1.63 g.) was dissolved in anhydrous pyridine (10 ml.). To this solution was added with occasional shaking and cooling, a solution of p-toluene-sulphonyl-chloride (1.92 g.) in anhydrous pyridine (10 ml.). The reaction mixture was allowed to stand at room temperature for 24-72 hours. Excess of pyridine was removed under reduced pressure. The residue was dissolved in water and extracted with ether. The ethereal extracts were dried and ether was removed on the steam bath. The residue (1.4 g.) was found to be the unchanged starting material by IR and NMR spectra.

1:5-Dimethyl-3-carboethoxy-4-hydroxy-piperidine (178).

1:5-Dimethyl-3-carboethoxy-4-piperidone (9.95 g.) was dissolved in methanol and cooled to  $0^\circ$ . To this solution, sodium borohydride (0.95 g.) was added in portions with stirring over a period of 7 minutes. The rest of the details are the same as those described for the reduction of 1:5-dimethyl-3-cyanomethyl-4-piperidone (151) to the corresponding

secondary alcohol (174). The residue was distilled affording 8.01 g. (80%) of 1:5-dimethyl-3-carboethoxy-4-hydroxy-piperidine solidified on standing and recrystallised from petrol, m.p. 90-2° (with softening at 79°).

$C_{10}H_{19}O_3N$  requires: C, 59.67; H, 9.52; N, 6.96%

found: C, 59.80; H, 9.50; N, 6.90%

The IR spectrum (film) showed a broad OH band from 3150-3500  $cm^{-1}$  and a broad ester CO band at 1725  $cm^{-1}$ . The NMR spectrum ( $CDCl_3$ ) showed an N-CH<sub>3</sub> singlet at 2.25 p.p.m., the C-CH<sub>3</sub> doublet centred at 1.05 p.p.m., the ester CH<sub>2</sub> quartet centred at 4.29 p.p.m. and the ester CH<sub>3</sub> triplet centred at 1.3 p.p.m. The hydroxyl proton appeared as a broad peak at 3.5 p.p.m. which disappeared on shaking with D<sub>2</sub>O.

1:5-Dimethyl-3-carboethoxy-4-chloro-piperidine (179) and 1:5-dimethyl-3-carboethoxy-tetrahydropyridine (180).

Thionyl chloride (6.75 g.) was added dropwise with stirring to a solution of 1:5-dimethyl-3-carboethoxy-4-hydroxy-piperidine (7.537 g.) in chloroform at room temperature. When the addition was complete, the solution was stirred for 25 minutes at room temperature. Excess of thionyl chloride and chloroform was removed under reduced pressure and at room temperature. The residue was dissolved in water, saturated with anhydrous sodium carbonate and extracted with ether. The ethereal

extracts were dried and the solvent was removed. The residue, being unstable, was converted to the unsaturated ester (180) on distillation.

A consistent analysis could not be obtained on the chloro-compound (179) and it did not form a picrate or hydrochloride.

The IR spectrum (film) showed the C-Cl band at  $730\text{ cm}^{-1}$  and the ester CO band at  $1725\text{ cm}^{-1}$ . The NMR spectrum ( $\text{CDCl}_3$ ) showed the C-CH<sub>3</sub> doublet centred at 1.02 p.p.m., an N-CH<sub>3</sub> singlet at 2.33 p.p.m., the ester CH<sub>2</sub> quartet centred at 4.28 p.p.m. and the ester CH<sub>3</sub> triplet centred at 1.31 p.p.m.

1:5-Dimethyl-3-carboethoxy-tetrahydropyridine (180) was also obtained when the reaction of the hydroxy-compound (178) with thionyl chloride was carried out in refluxing chloroform or benzene saturated with hydrogen chloride. The tetrahydropyridine (180) darkens on standing. A consistent analysis could not be obtained on the compound (180) and it did not form a picrate or hydrochloride.

The IR spectrum (film) showed a broad ester CO band at  $1710\text{ cm}^{-1}$  and a very sharp band at  $1658\text{ cm}^{-1}$  due to C=C, presumably due to the  $\alpha:\beta$ -unsaturated ester. The NMR spectrum ( $\text{CDCl}_3$ ) showed an N-CH<sub>3</sub> singlet at 2.4 p.p.m., a C-CH<sub>3</sub> doublet centred at 1.08 p.p.m., the ester CH<sub>2</sub> quartet centred at 4.28 p.p.m., the ester CH<sub>3</sub> triplet centred at 1.3 p.p.m. and the vinyl hydrogen appeared as a rather broad peak at 6.96 p.p.m.



1:5-Dimethyl-3-cyanomethyl-4-chloro-piperidine (176).

1:5-Dimethyl-3-cyanomethyl-4-hydroxypiperidine (9.33 g.) was dissolved in chloroform. To this solution, thionyl chloride (9 g.) was added with stirring so as to keep the solution refluxing gently. When the addition was complete, the reaction mixture was heated under reflux for one hour. Excess of thionyl chloride and chloroform was removed under reduced pressure. The residue was dissolved in water, saturated with anhydrous sodium carbonate and extracted with chloroform. The chloroform extracts were dried and the solvent was evaporated under reduced pressure. The residue was distilled affording 8.31% (80%) of 1:5-dimethyl-3-cyanomethyl-4-chloropiperidine, b.p. 75-7°/0.1 mm.

$C_9H_{15}N_2Cl$  requires: C, 57.91; H, 8.04; N, 15.01%

found: C, 58.11; H, 7.98; N, 14.91%

The IR spectrum (film) showed a sharp C-Cl band at 730  $cm^{-1}$  and a sharp CN band at 2250  $cm^{-1}$ . The NMR ( $CDCl_3$ ) showed an N-CH<sub>3</sub> singlet at 2.33 p.p.m., the expected C-CH<sub>3</sub> doublet gave a sub-splitting pattern centred at 1.08 p.p.m.

Attempted preparation of the malonate derivative (177).

a) Diethyl malonate (4.80 g.) was converted into the sodium salt with sodium ethoxide obtained from sodium (0.50 g.) and absolute ethanol (75 ml.). To this solution was added 1:5-dimethyl-3-cyanomethyl-4-chloropiperidine (3.73 g.) with stirring. The solution was heated under reflux for 14 hours. Excess of ethanol was removed under reduced pressure.

The concentrate was diluted with water and extracted with ether.

The ethereal solution was then extracted with 10% hydrochloric acid.

The acid solution was washed with ether, made alkaline, saturated with anhydrous sodium carbonate and extracted with ether. The ethereal extracts were dried and the solvent was removed on the steam bath. The residue (3.5 g.) was found to be the unchanged starting material by IR and NMR spectra.

b) Using the same quantities of the reactants as in (a), except for sodium hydride (50% dispersion, 1.2 g.) instead of sodium, the reaction was carried out in refluxing dimethoxyethane for 4 days. Working up the reaction mixture as before, the unchanged starting material was obtained.



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